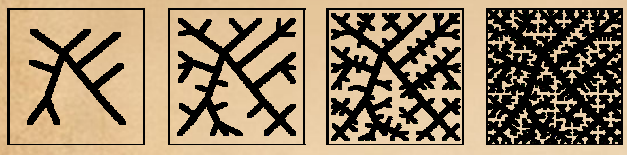
Marc E. Gottlieb, MD, FACS
A Professional Corporation

PLASTIC & RECONSTRUCTIVE SURGERY
Board Certification ••• ••• ••• *Plastic Surgery* ••• *Hand Surgery* ••• *General Surgery*



Specializing in the treatment, reconstruction, and management of
Acute and chronic wounds • Diseases and defects of the soft tissues • Injuries, diseases, and defects of the hand and extremities • Defects of the head and trunk

Office: 1415 N. 7th Avenue • Phoenix, AZ 85007 **Phone 602-252-3354** **Fax 602-254-7891** **megott@arimedica.com**

Marc E. Gottlieb, MD, FACS

1415 N. 7th Avenue
Phoenix, AZ 85007

Phone 602-252-3354
Fax 602-254-7891

megott@arimedica.com

WOUND HEALING – A CLOSED LOOP CONTROL SYSTEM

Original presentation May 15, 2006, Scottsdale, AZ
at the annual meeting of the Wound Healing Society

This is the original poster, reformatted for standard paper layout.
Additional annotations pending.

WOUND HEALING – A CLOSED LOOP CONTROL SYSTEM

Marc E. Gottlieb, MD, FACS Phoenix, AZ

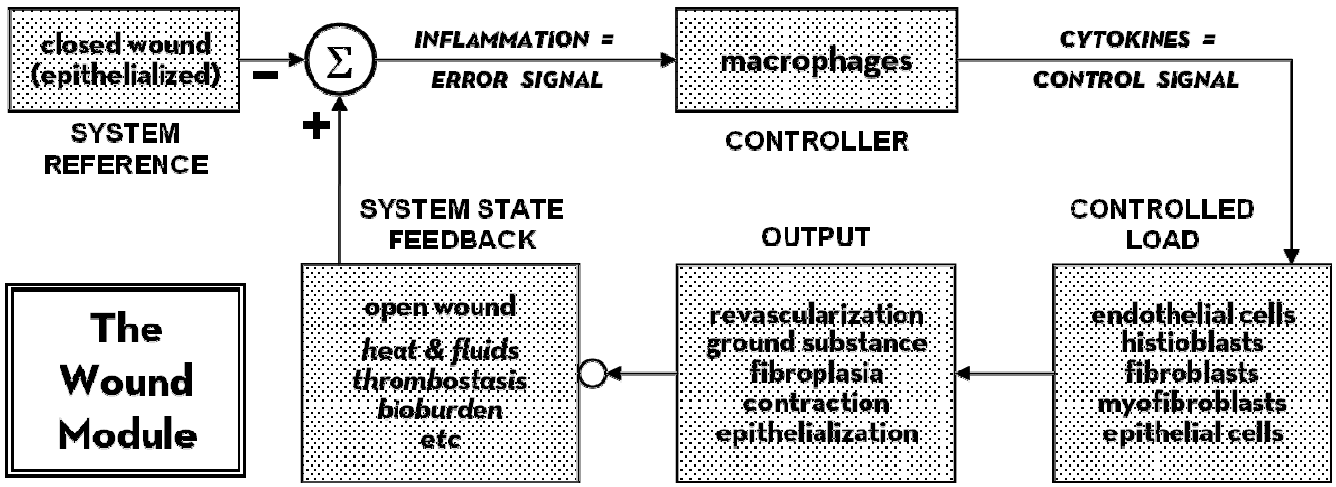
Presented at the Woud Healing Society Annual Meeting, Scottsdale, AZ, May, 2006

Abstract

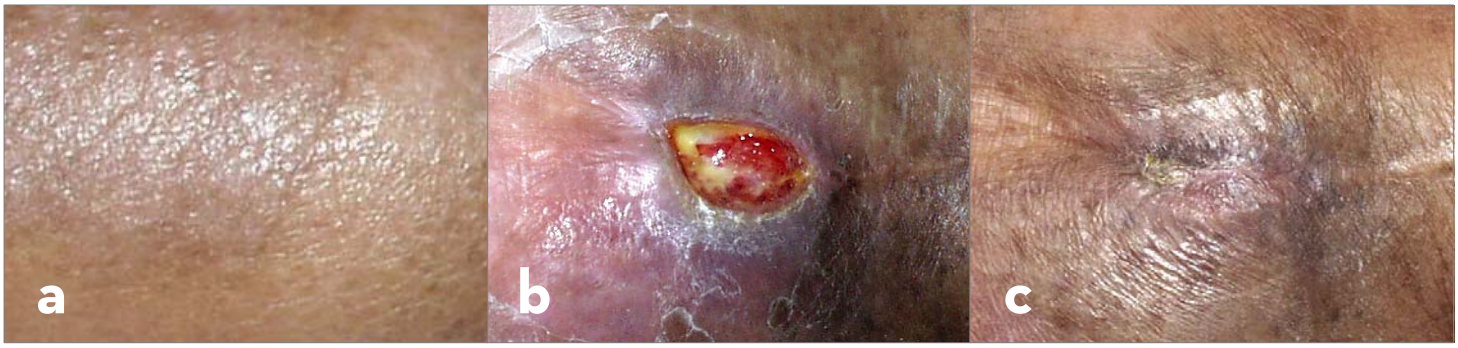
The Problem. Physiology research of the past century has depended on linear models of dependent-versus-independent parameters in an otherwise invariant environment. Classic wound research has characterized hundreds or thousands of such cellular and chemical interactions. The problem is that, while linear dependencies are important, the mutual behavior of three or more elements cannot be assessed analytically (rather, by iteration). The past few decades have seen the advent of non-linear dynamics and control science. These disciplines provide the tools for understanding the behavior of N-element systems.

Wounds are a complex non-linear multicontrol system. Injury, pathology, chronicity (chaos), and the therapeutics of wounds, including contrary or contradictory behaviors can be readily explained when wounds are understood as a System, rather than as just a collection of dual-element linear interactions. While sick or divergent wounds are subject to many perturbations or additional layers of feedback and control, the quintessential intrinsic machinery of wound healing – the "Wound Module" of proliferative post-inflammatory wound repair – functions as just a single control loop. This presentation will introduce basic concepts of closed loop control systems, and then characterize the Main Control Loop of normal physiological wound repair.

The wound control system is composed of these elements: The system state is the open wound and its conditions. It is compared (Σ) to a reference, normal epithelialized tissue. Variances generate an error signal in the form of inflammation. This activates macrophages which are the system controller. They in turn generate a control signal in the form of cytokines. The controlled load is the group of local responder cells. Their output are the elements of histogenesis, which modify the state of the system, which then feeds back to the loop at the summing point. Any discussion or research of the collective behavior of a wound must acknowledge this basic control system.



WOUNDS AND CONTROL



Wounds are a closed loop control system

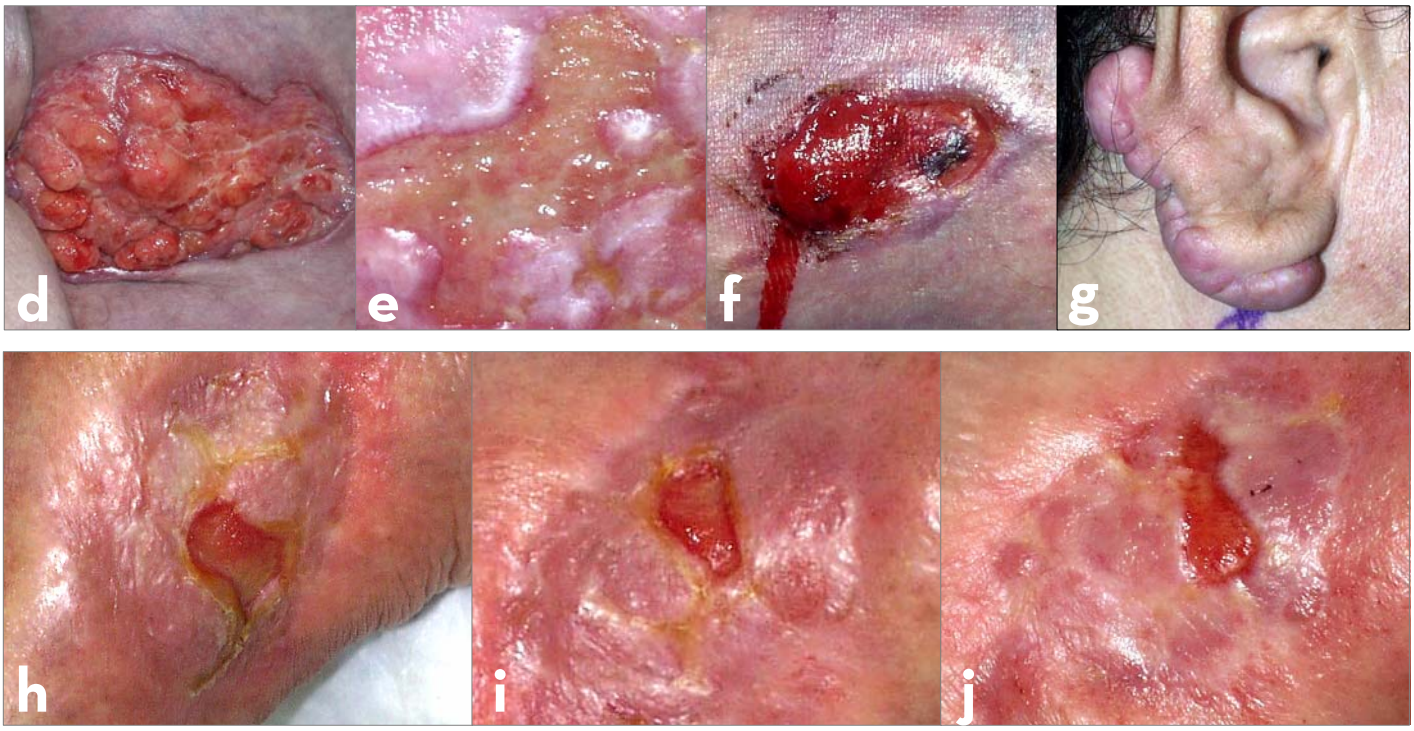
Normal wound healing is a purely reactive and highly controlled system. Consider these illustrations:

a. Normal skin from a healthy subject. It will not change. It will not spontaneously start wound healing.
b. Same subject. Wound healing is a reserve system. How does it know to start? Injury triggers the process.
c. The same wound healed. Once the wound is closed, the healing process ceases. How does it know to stop?

This example is so mundane and obvious as to seem trivial and silly, but it is profoundly important. Normal wound healing has controls. Responding only if perturbed, it restores the system to a defined reference.

The wound must turn on its relevant "machinery", sense its own evolving status, compare itself to "normal", and then cease when the process is complete. Reactivity, feedback, reference, control. The wound is a non-linear closed-loop feedback control system. These concepts underlie a true understanding of how a wound heals – its physics and dynamics – and how it goes awry, and how it can be treated when the machine is impaired.

WOUNDS AND CONTROL



Examples where the machine is unregulated, broken, or on an atypical attractor:

d. No healing. Wound of posterior thigh, below gluteal crease. The patient has advanced active rheumatoid, on cyclophosphamide and steroids. After 6 months, each adipose lobule is still individually seen. There is no fibroplasia whatsoever, and only a nominal minimum of angiogenesis, with no contraction nor epithelialization.

e. No healing. A back reconstructed with collagen-gag matrix (Integra). The matrix arrests inflammation and normal wound healing (instead inducing embryonic histogenesis). Epidermis will still migrate from margins, but "granulation tissue" and mesenchymal elements of healing will not appear (a desirable property in this case).

f. Healing improperly. In this leg wound, granulation tissue has become hypertrophic, a "pyogenic granuloma". Normal controls or activity in the wound have gone awry, favoring raw mesenchymal proliferation rather than contraction and epithelialization.

g. Excess healing. This keloid is another unregulated "attractor" for the original wound. Either fibroplasia has become unresponsive to normal controls, or some abnormal stimulus is present, causing abundant excesses of the latter phases of wound repair.

h-i-j. Chaotic. H-to-i is a 1 month interval, then 4 months to j. From exam to exam, this ankle wound has no net change. Sometimes a bit smaller, sometimes a bit bigger, there is no real movement, neither better nor worse. It is in a chaotic "orbit", a standard permissible behavior of complex non-linear systems (such as The Wound).

WOUNDS AND CONTROL

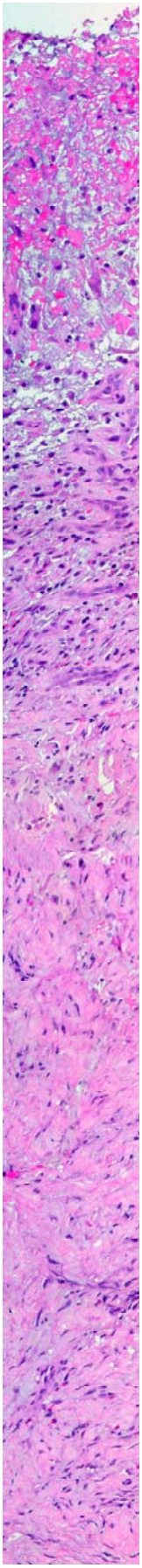
The Wound is a Complex Machine - it must be analyzed as such. Welcome to the century of The System.

Old science: Physiology of the 20th century, an age of biochemical discovery, was grounded in chemistry. It focused on one-to-one reactions and kinetics between any two chemicals or bio-parameters. It promulgated "homeostasis", predicated on chemical concepts of reaction equilibrium. But biological systems do not really work that way. They are built from many simple elements of that nature, but they have MANY inter-operative elements. Three-body (and all higher N-body) problems cannot be solved by simple balanced equations.

New science: At the start of this century, we have decoded the genome. How do gene products interoperate to make Life? To understand Complex Systems, principles are needed from Physics and Engineering. The wound is a paradigm of a complex N-body system. Accurate understanding of its many behaviors must start with a meaningful model of the Machine, the System, and not just its chemistry-oriented individual components.

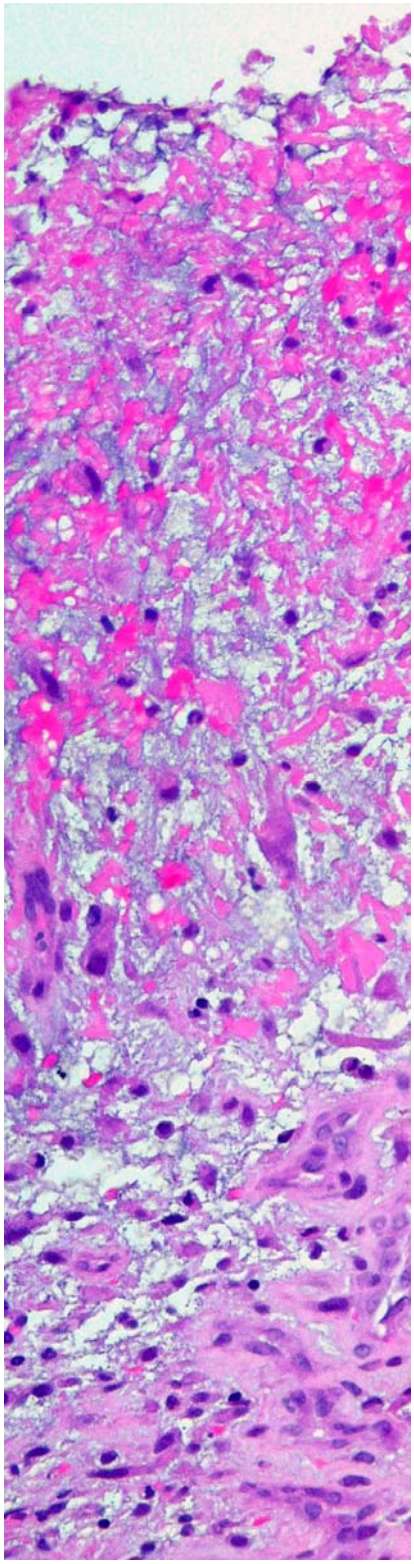
To understand why healthy wounds heal normally, or why the above cases were abnormal, the next two panels will start with an explanation of the normal wound machine, then explain the basics of control and dynamics.

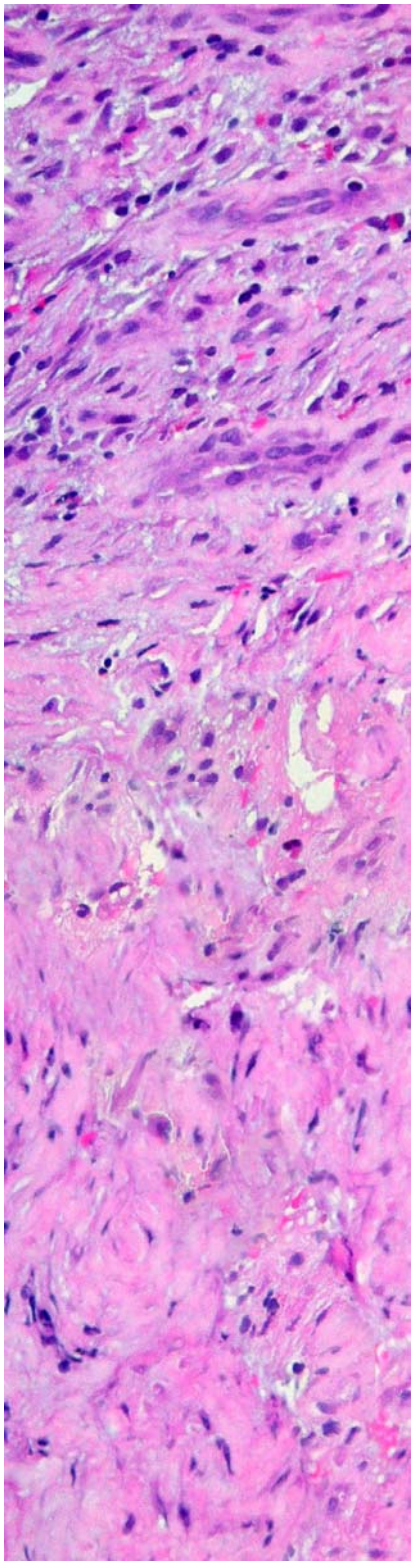
THE WOUND MODULE

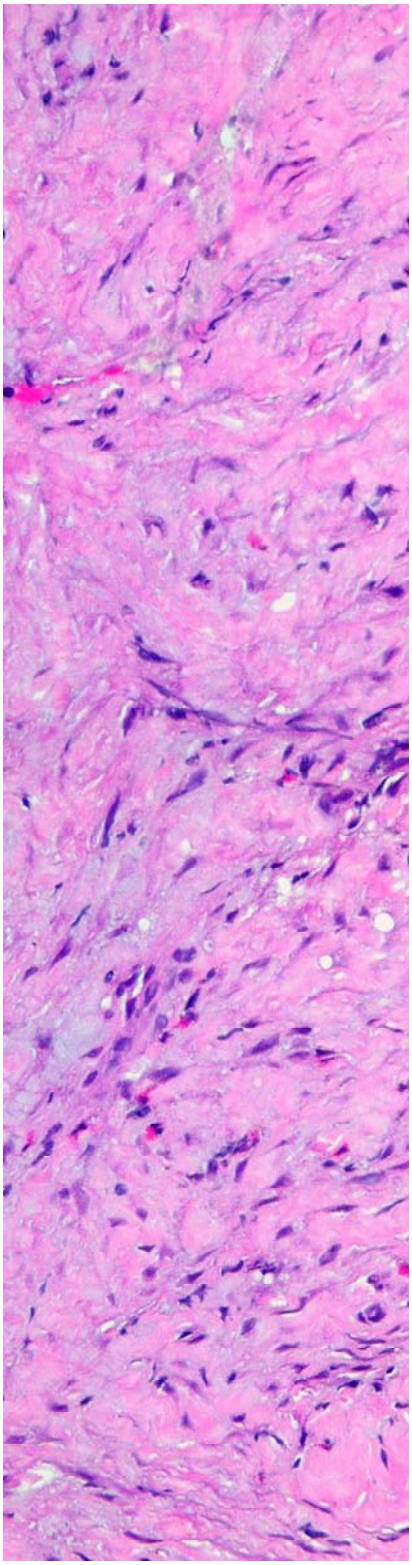


The wound module is the integrated set of cells and chemicals which heal a wound.

Shown is a wound, its histology and clinical features, illustrating the essential components of the wound module. As a complex system, it is desirable to have a standard schema to explain these elements and their interactions.

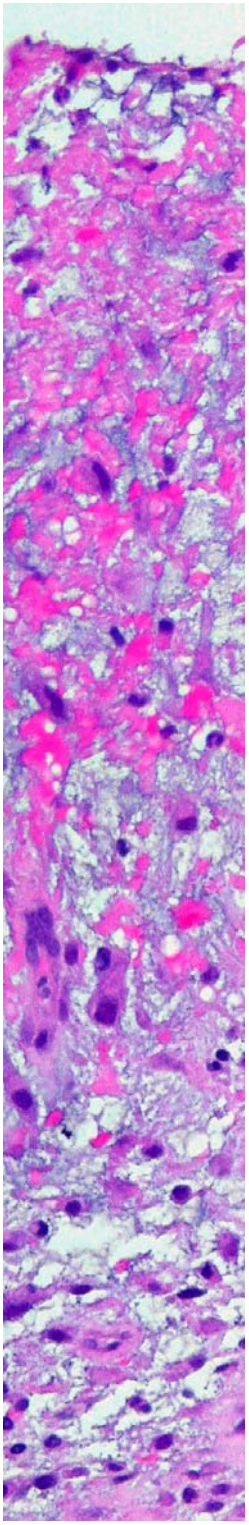


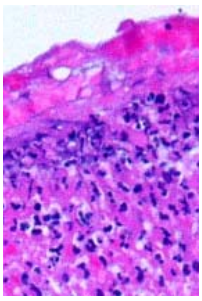


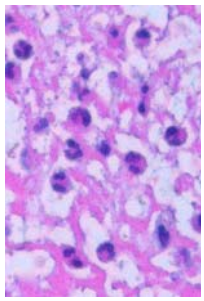


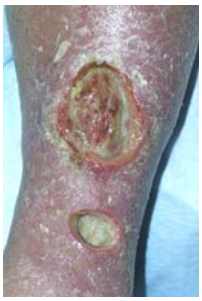
THE WOUND MODULE

The wound module is the integrated set of cells and chemicals which heal a wound.
Shown is a wound, its histology and clinical features, illustrating the essential components of the wound module. As a complex system, it is desirable to have a standard schema to explain these elements and their interactions.

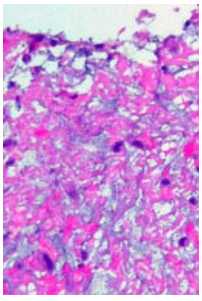


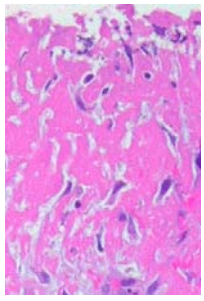


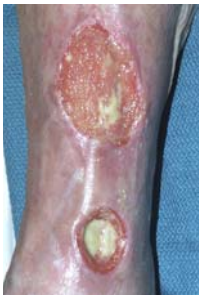




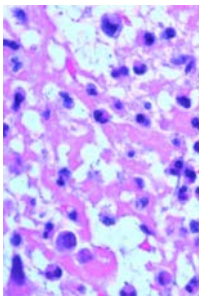
0 - Active injury and inflammation. Inflammation is the initial response to injury, to contain damage, clear debris, and prepare for repair. Inflammation and repair are integrated sequential processes. **a -** Wound surface, with intense neutrophils, plasma exudates. **b –** Neutrophil close-up. **c –** An injured leg, inflamed, not healing.

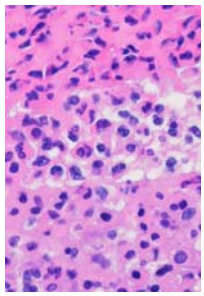


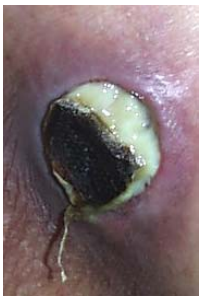




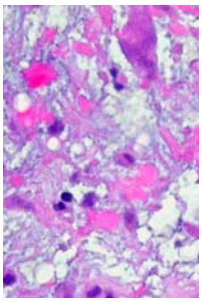
1 - Inflammation subsides. While inflammation induces repair, it is also inherently injurious, and when acute and intense, it suppresses repair. It must subside for repair to proceed. **a, b -** Wound surfaces well cared for, free of neutrophils and excess plasma exudates. **c -** The same clinical case after 2 weeks of care, now healing.

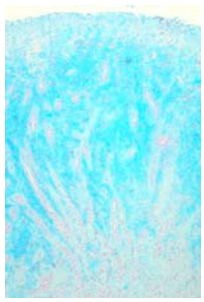


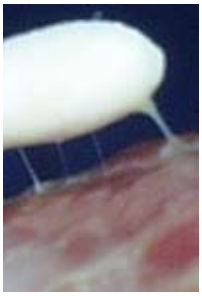




2 - Macrophages, eschar separation. Macrophages are recruited and transformed by inflammation. **a -** They appear as enlarging mononuclear cells in the inflammatory layer. **b -** They have two functions in a wound. The first is eschar separation, seen here as the central cleavage. **c -** Eschar separation seen clinically.

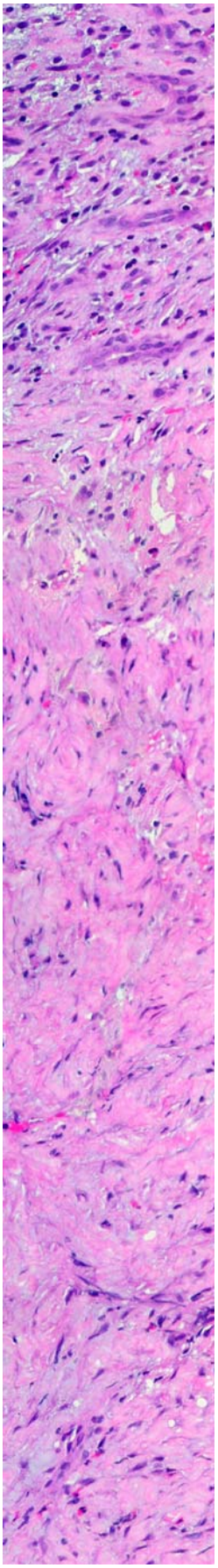


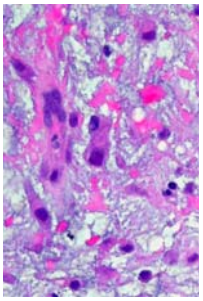


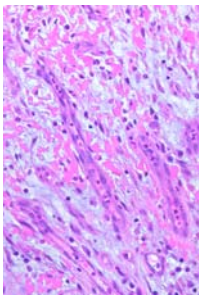


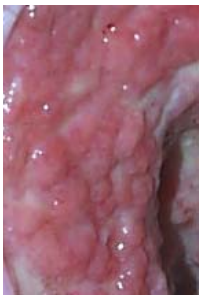
3 - Aminoglycan ground substance. Aminoglycans form under (after) the inflammatory layer, an "ether" in which repair cells will migrate, substance where there is no structure. **a –** The ground substance, free of collagen. **b –** Alcian blue stain showing this layer. New vessels, fan-shaped, are migrating from below. **c –** Normal wound mucus.

THE WOUND MODULE

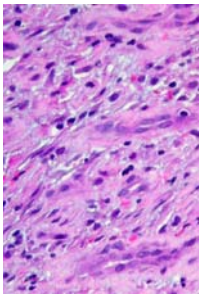


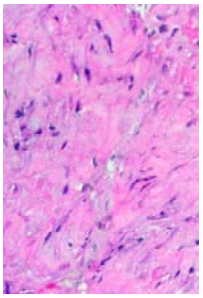


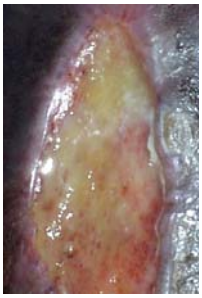




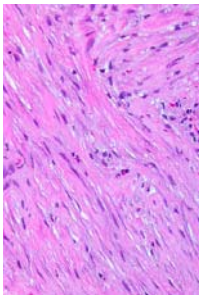
4 - Angiogenesis. The second macrophage function is to make growth factors which stimulate local cells to do the repair functions. First is the attraction of new vessels. **a –** Dissociated angiocytes migrating and reassembling in the aminoglycan layer. **b –** New vessels fully reorganized in older layers. **c –** "Granulation tissue".

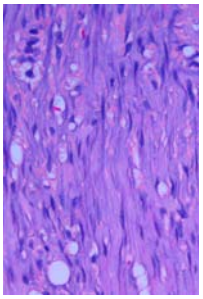


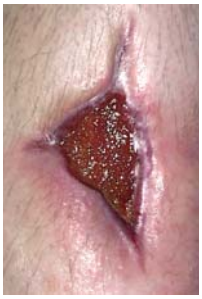




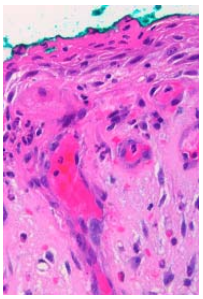
5 - Fibroplasia. Once new vessels restore a good environment, fibrous cells start to "pour the concrete" of new body substance. **a –** Youngest new fibrous cells among new vessels, just starting to make faint collagen. **b –** Advanced collagen production. **c –** In a wound with atrophic upper layers, older, deeper fibrosis is easily seen.

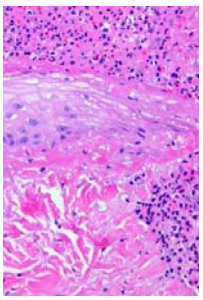


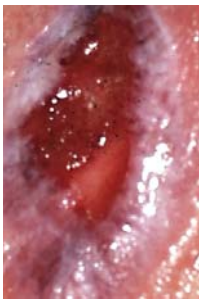




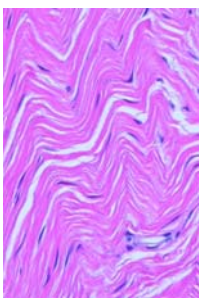
6 - Contraction. Ongoing fibroplasia begets denser, less compliant scar. Some of it will actively contract, due to myofibroblasts. **a –** Dense new scar, with typical features responsible for its mechanical properties. **b –** Dense, highly cellular scar from a "genu" of contracture at a wound margin. **c –** A wound actively closing by contraction.

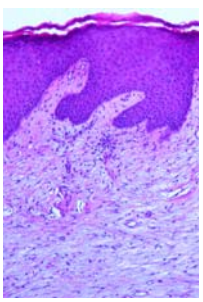


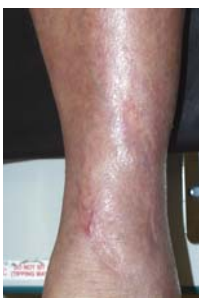




7 - Epithelialization. A wound is nominally closed when epithelium is completely continuous, mesenchyme fully sequestered from ambient world. Epithelium only migrates over other healthy wound module components. **a –** Epidermis at edge of a healthy wound. **b-** Advancing epithelium cleaving eschar. **c –** Clinical view.





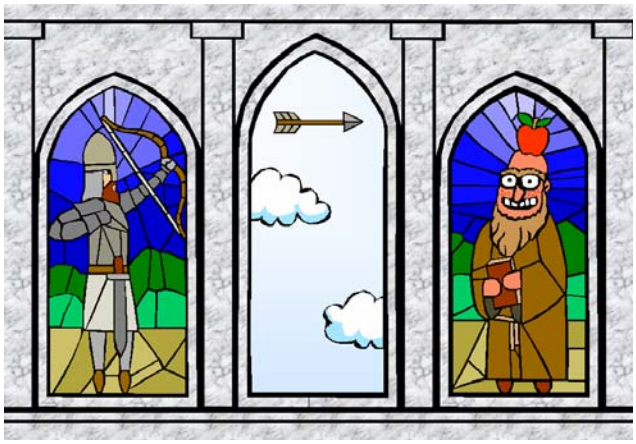


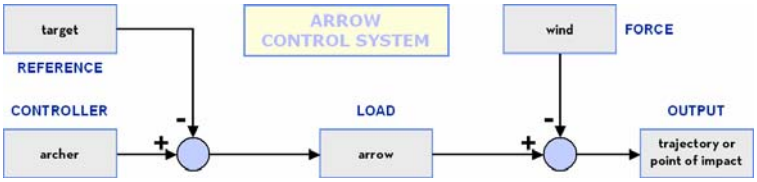
8 - Maturation. Once epithelialized, wounds mature, a slow process of remodeling a young scar back toward host histology. **a –** Mature scar returning to dermis or fascia. **b –** Epidermis maturing, and forming a lamina propria (papillary dermis). **c –** The same leg as above, healed and mature.

CONTROL AND NON-LINEARITY

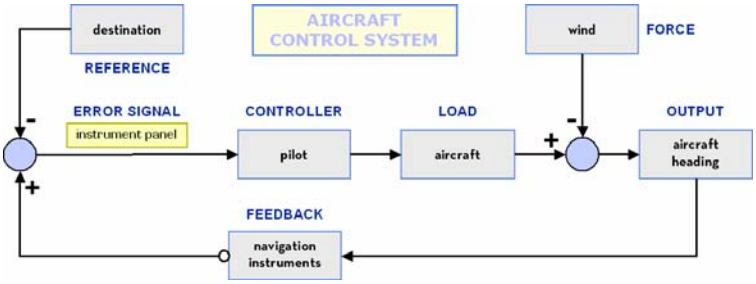
The need for control

The purpose of "control" is for a system to hold itself to a desired output, state, or attractor. Key to control is feedback, the ability to sense the system state or output, which then drives an error correcting mechanism.

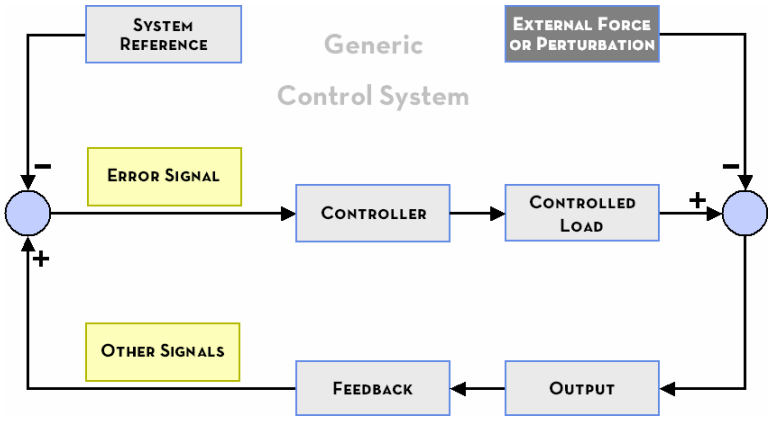




The arrow: There is no feedback – this system is open loop. Once airborne, nothing can assess nor correct its course. Open loop systems must be calibrated (aimed), and if a gust of wind or anything upsets that calibration, the system misses its mark.



The airplane: The plane is steered, not aimed. Its pilot and flight controls assess and correct the plane's heading. This is a system of feedback and closed loop control, and it permits the system to reach its target.

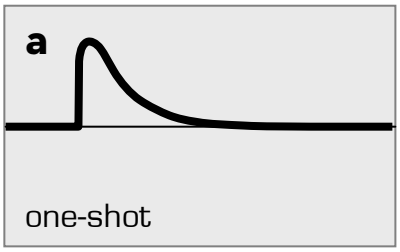


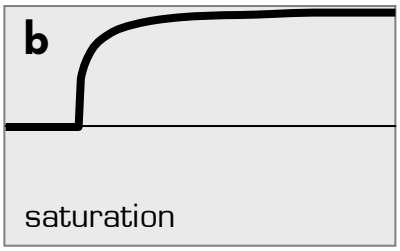
Closed loop control systems: They react to correct any difference between their actual state and a reference value. They have these basic elements:

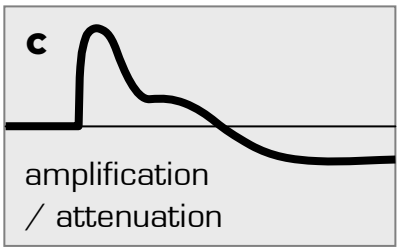
Reference: The target the system works to maintain.
Controller: Mechanism to implement corrections.
Load: Element that is acted on by the controller.
Output: Element or system state that is monitored.
Feedback: Method to report current system state.
Signals: Information or trigger intermediaries.
Nodes: Combinatorial points that yield values.

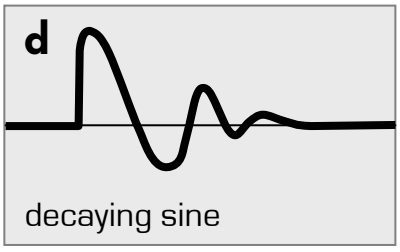
Forces: Extrinsic perturbations which force response.

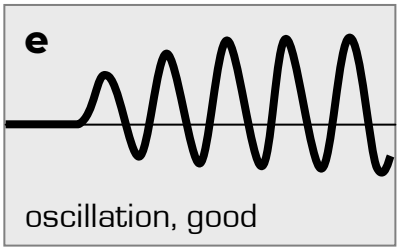
CONTROL AND NON-LINEARITY

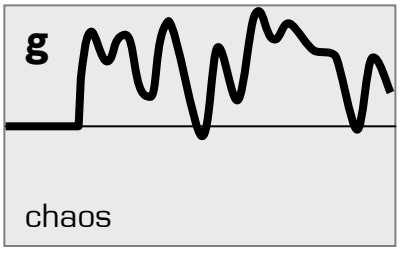












Closed loop control systems:

They react to correct any difference between their actual state and a reference value. They have these basic elements:

Reference: The target the system works to maintain.
Controller: Mechanism to implement corrections.
Load: Element that is acted on by the controller.
Output: Element or system state that is monitored.
Feedback: Method to report current system state.
Signals: Information or trigger intermediaries.
Nodes: Combinatorial points that yield values.
Forces: Extrinsic perturbations which force response.

Control responses:

A control system monitors itself. If it senses variances from reference, it tries to counteract them, pulling back in the opposite direction, trying to keep as close as possible, as smoothly as possible, at reference or target level. This can work well, or there can be instabilities. Here is a sampler of possible responses.

a. One-shot. Perturbation is corrected by a smooth return to reference (linear, exponential, etc). (This is the response of a healthy wound to simple injury.)

b. Control may fail or be over-whelmed, the system saturating or extinguishing at its extrema. (The wound response to severe inflammation or active disease.)

c. Blunted or exaggerated reactions can result in over- or under correction. (Formation of pyogenic granuloma or keloid.)

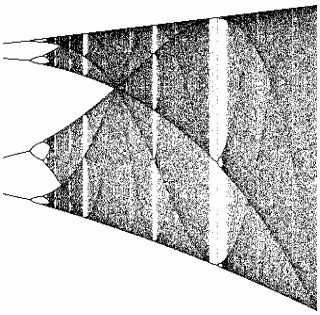
d. Compensatory responses can over-shoot target, resulting in dampened sine waves on the way back to reference.

e. Overshoot can go back-and-forth, creating oscillations. This can be intentional or desirable, as in radio wave circuits. (e.g. a bee's wingbeat, or a heartbeat.)

f. Unintended, exaggerated, and multi-harmonic oscillations are the bane of good control. (e.g., Parkinson or cerebellar tremor.)

g. In multi-control systems, instabilities can be erratic, non-harmonic, non-analytical – aka chaos. In wounds, the state may return to baseline (closed), but still be unstable and re-ulcerate. (Most chronic wounds.)

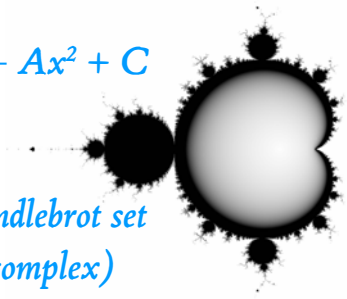
CONTROL AND NON-LINEARITY



$x \leftarrow Ax(1-x)$

Logistical plot (real)

$x \leftarrow Ax^2 + C$

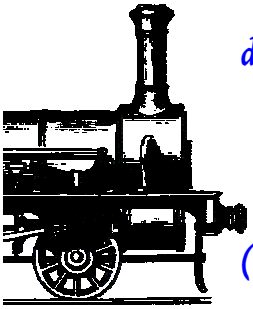


Mandlebrot set (complex)

Iterations of x²

not your father's parabola

Non-linearity: Non-linear systems are recursive, self-dependent, iterative, their future value or state dependent on their current state. They have the general form **x = f(x)** or **x ← f(x)**. Feedback means non-linearity. Any control system, including the wound, is non-linear. The examples show that even the simplest face-value systems can have very complex behaviors when iterated or non-linear.



$d\varphi = v\partial r + r\partial v$

$\partial\varphi = v\partial r$

$\partial\varphi = r\partial v$

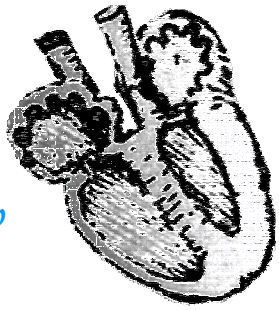
Linear pump (sum of partials)

$d\varphi = v\partial r + r\partial v$

$v = f(\varphi, r)$

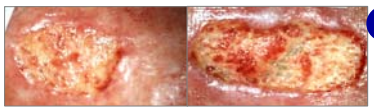
$r = f(\varphi, v)$

Non-linear pump (non-analytical)

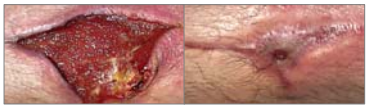


output (φ) = rate (r) x volume (v)

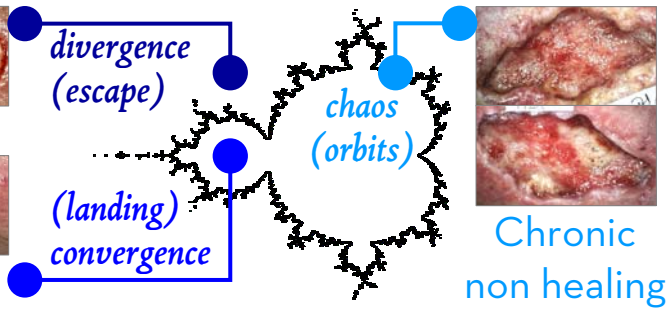
N-body systems and multicontrol: Flow in the piston pump is related to mutually independent rate and volume – a sum of two 2-body functions. In the heart, **r**, **v**, φ are all mutually regulatory. No system of analytical math (equation based) can solve 3-body systems where each element is a function of all others. Multicontrol processes, such as a wound, are all N-body systems, in which complex behaviors are not predictable, and iteration and the tools of non-linear dynamics are the required methods.



Active ulceration



Active healing



Chronic non healing

Chaos: Non-linear systems are deterministic, but their dynamics are often complex and non-analytical. Unlike the plane which follows a relatively smooth course, many non-linear systems seem erratic and unsettled, jumping value to value in seemingly unpredictable ways. This is mathematical chaos, the "in between" state of complex systems.

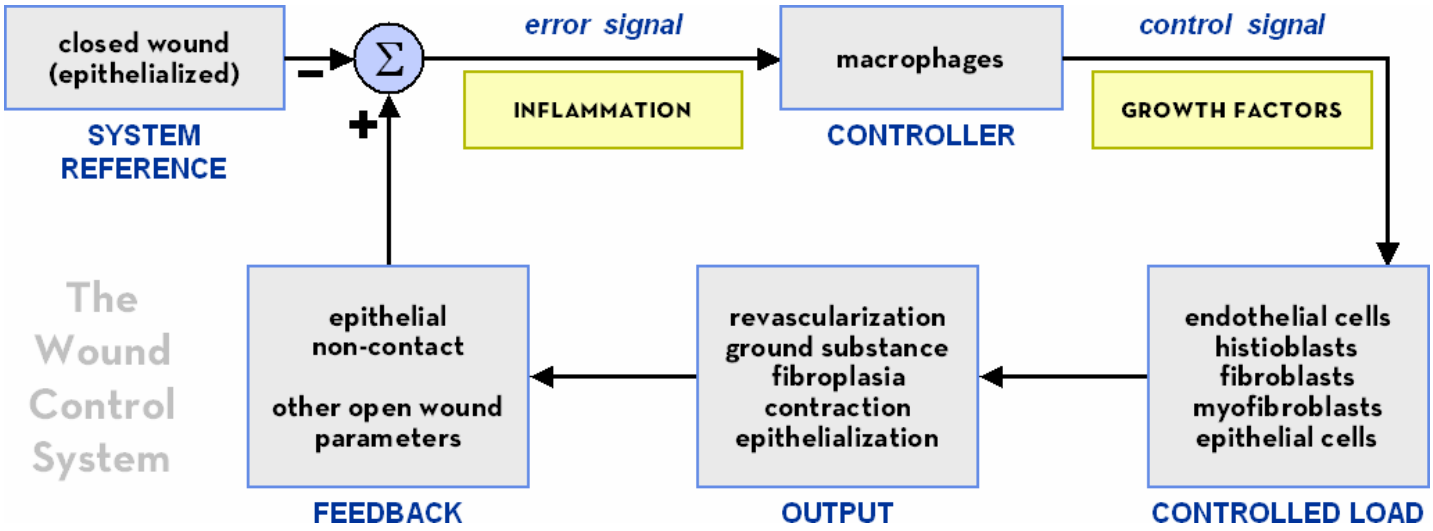
Control and non-linearity in wounds:

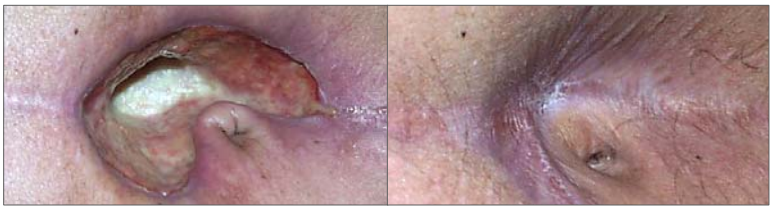
Nature and biology have many complex multi-element self-targeting non-linear systems, with a wide range of potential dynamical behaviors. The Wound is one of them. Wounds converge on the desired state when healthy, but when sick, divergent and chaotic behaviors appear.

THE WOUND: THE MAIN CONTROL LOOP

The wound is a non-linear controlled machine.

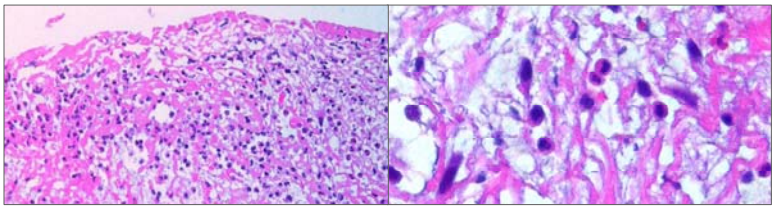
The proliferative module of normal post-inflammatory wound healing must be regulated as to when to turn on, how much output to create, and when to cease. This control or regulation is a non-linear process based on a closed feedback loop having all of the elements of any well-controlled machine.





When the wound is closed, fully re-epithelialized, proliferative wound healing ceases – it knows when to stop.

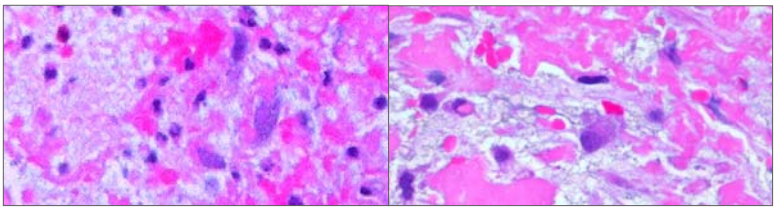
System reference – a closed wound.
The system reference is a closed wound, meaning continuously epithelialized, the mesenchyme fully sequestered from the environment. This is what the wound control loop will work to restore when the system state has been disturbed.



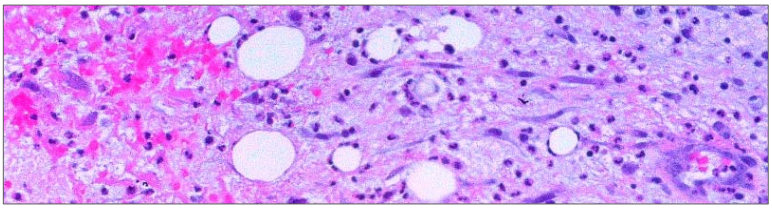
Inflammation at wound surface has many functions. The mononuclear cells are key to turning on wound healing.

Error signal – inflammation.
When a detector (summing node) senses a variance from reference state, it will error signal the wound healing system via inflammation. Inflammation is its own complex control system, but regarding wound healing, it is a black box whose input is an open wound, and whose output is a wound healing switch.

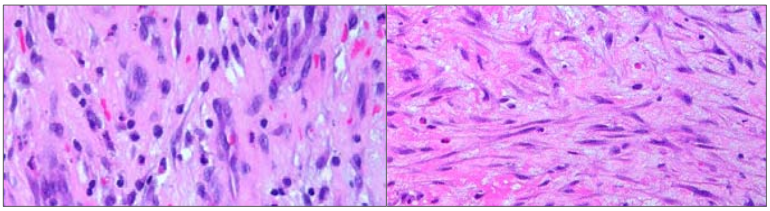
THE WOUND: THE MAIN CONTROL LOOP



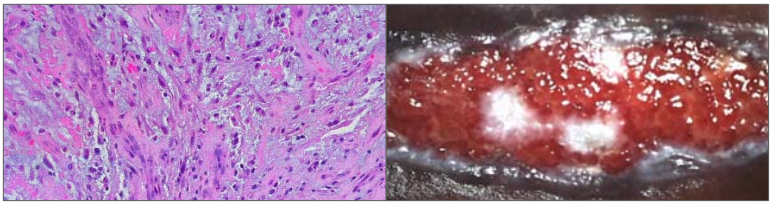
Macrophages are large transformed monocytes in the wound's upper inflammatory and plasma protein layers.



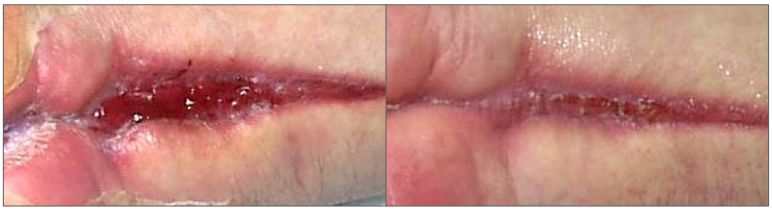
Chemotropic attraction is easily seen as angiocytes stream away from parent vessels toward stimulus cells.



Angiocytes & histioblasts (left), more mature fibroblasts (right), proliferating due to macrophage growth factors.



Ground substance, vessels, connectives, contraction, epithelialization = the products of the wound module.



When epithelium is continuous, the wound is closed, and the loop diverts to the chronic maturation phase.

Controller – macrophages.
Macrophages are delivered and activated by inflam-mation. Their afferent function is to remove debris. Their efferent function to muster and manage local wound healing cells. They do not themselves heal the wound, but as the managers of the repair machinery, they are the system controller.

Control signal – growth factors.
The macrophage controllers issue their orders by making growth factors. These include PDGF, TGFs, FGFs, EGFs, TNF, Ils, and related peptides. Their effect is to transform and attract local progenitor cells into a state of active histogenesis, including mitosis, migration, and phenotypic differentiation.

Controlled load – responder cells.
System load is the set of cells activated by macro-phages. Angiocytes answer first, arising from nearby vessels, to make new vessels. Then come histio-blasts, derived from pericytes and other tissue and marrow derived stem cells, becoming differentiated output-producing fibroblasts and myofibroblasts.

Output – proliferative wound module.
System output is the regenerative and reparative components of the proliferative wound module, made by the load cells. Ground substance, then vessels, then connective proteins appear, leading to a physical substance which restores body continuity. Contraction and epithelialization follow, for closure,

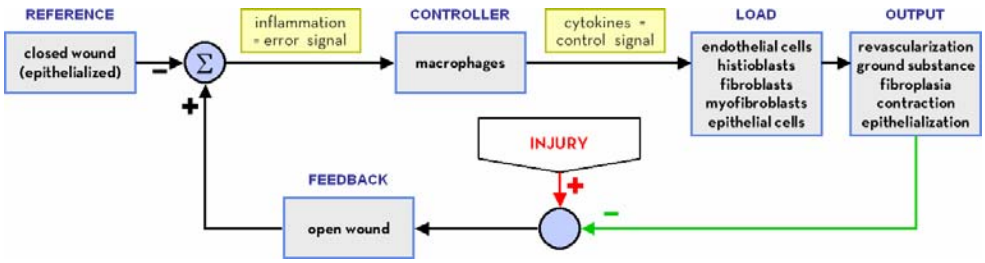
Feedback – open wound.
Open wounds have undesirable attributes (e.g. fluid loss, bioburden, continuing inflammation) which let the node measure variance of open versus closed wound. Continuous contact, sensed by free-margin epithelial cells, might be another mechanism. The common effect is to drive more inflammation.

MODELING THE NORMAL WOUND

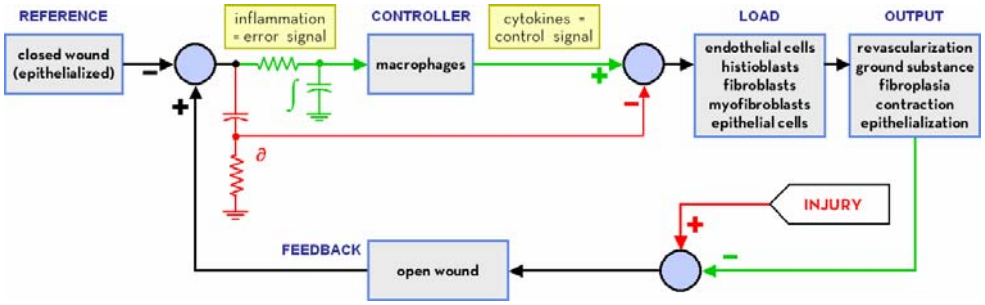
The wound machine, its elements and states, can be diagrammed.

There are countless chemical, cellular, and biophysical forces acting and reacting in a normal wound. By having a standard model and control loop to describe the core dynamics of any wound, the model can be put into service to represent, analyze, or explain selected elements or system components.

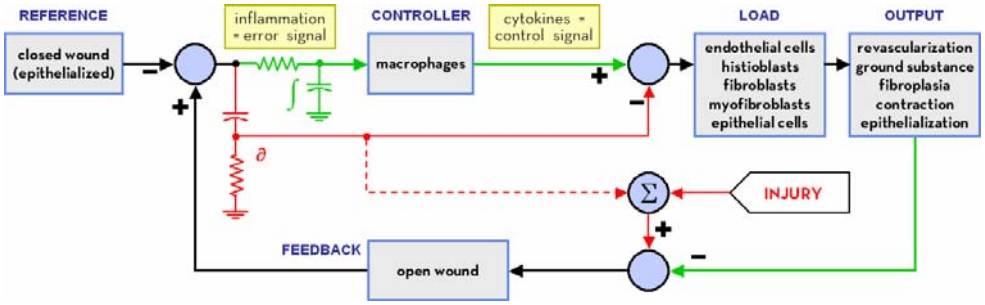
The chronic active wound. The core control loop in the prior panel is an implied one-shot, how the system responds to a one-time incidental injury, with no further perturbation. What if there is ongoing injury, due to an underlying illness or repetitive trauma? A simple modification introduces this additional element.



Active injury: The control loop's output lessens "open wound". Active injury, which creates more open wound, can be summed into the loop at the node shown.



Inflammation 1: Inflammation induces a wound module, but classic physiology tells us that acute inflammatory mediators also inhibit healing (conserv-ing resources; why inflamma-tion must abate before active repair is possible). To model this, split inflammation: an integrator gradually builds macrophage mass, ensuring robust healing at the right time; a differentiator branch transiently suppresses active healing during "flare-ups".

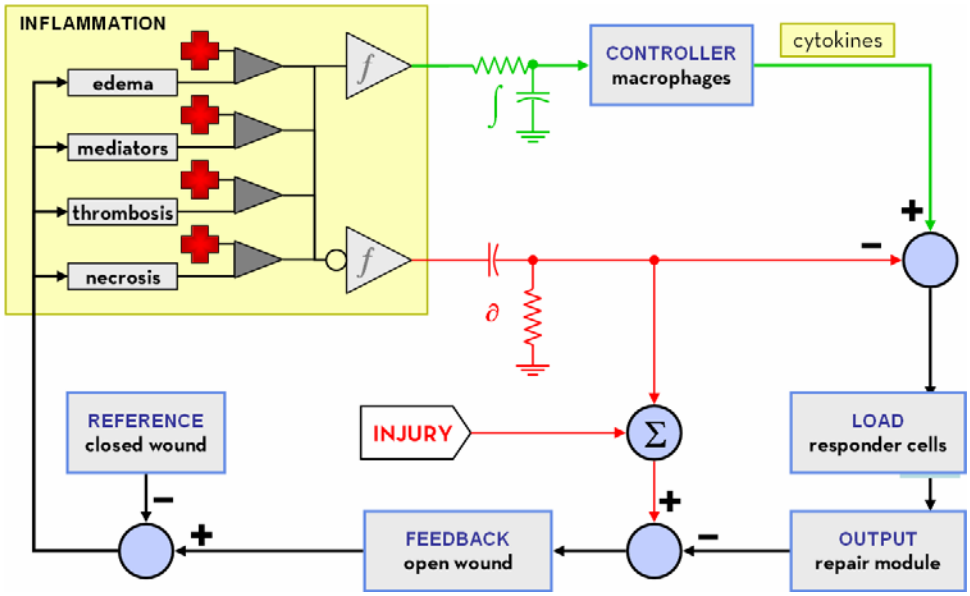


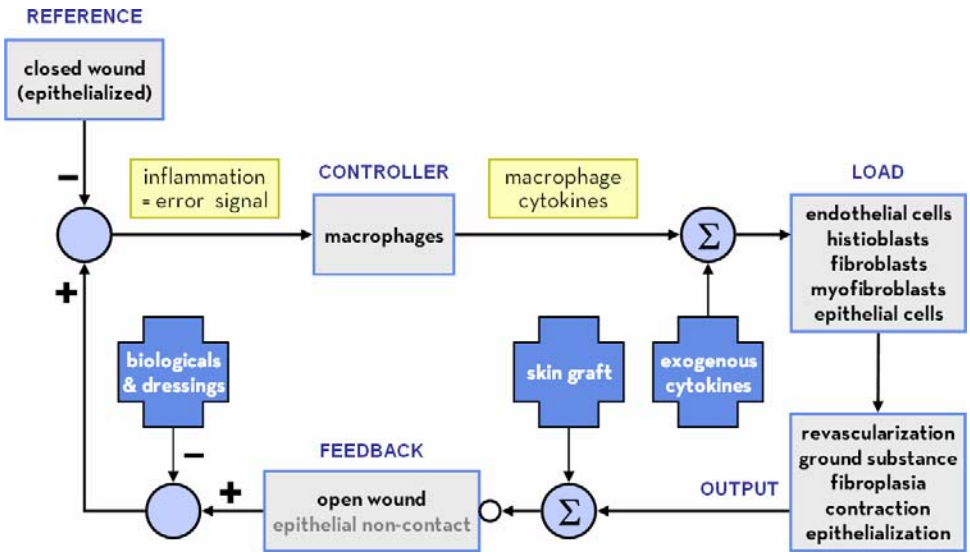
Inflammation 2: Intense inflammation is itself injurious and ulcerative, modeled by summing part of inflammation into the injury node.

MODELING THE NORMAL WOUND

The wound machine, its elements and states, can be diagrammed.

There are countless chemical, cellular, and biophysical forces acting and reacting in a normal wound. By having a standard model and control loop to describe the core dynamics of any wound, the model can be put into service to represent, analyze, or explain selected elements or system components.





Exogenous cytokines: Pharmaceuticals, such as PDGF, mimic macrophage activity, and sum into their node. **Skin grafts:** These and other operations, which directly restore epithelium, sum into the output node. **Biologicals:** These and special dressings, which do not restore epithelium but have a comparable biological effect, sum into the feedback node, reporting to the system that the wound is acting as though it is closed.

Basic wound therapies.

There are several classes of wound therapeutics, starting with basic modalities to correct injury, inflammation, and adversities, so that repair processes can proliferate and function. These "red crosses" – hygiene, debridement, edema control, etc. – are added as inverting inputs to counteract components within the inflammation "black box". Inflammation has two output stages, through filters *f*, which select various acute and chronic elements, to have them serve the two main functions of protect-the-host-but-suppress-healing versus active healing.

Wound healing therapies.

Another class of wound therapies are those modalities that stimulate repair. Most of these are technology based, expensive, and meant to be used only after initial therapies have controlled injury and inflammation. Unlike the basics, which counteract injury and inflammation, these treatments have a direct effect on the intrinsic engine of repair and the wound healing control loop. Three examples are shown.

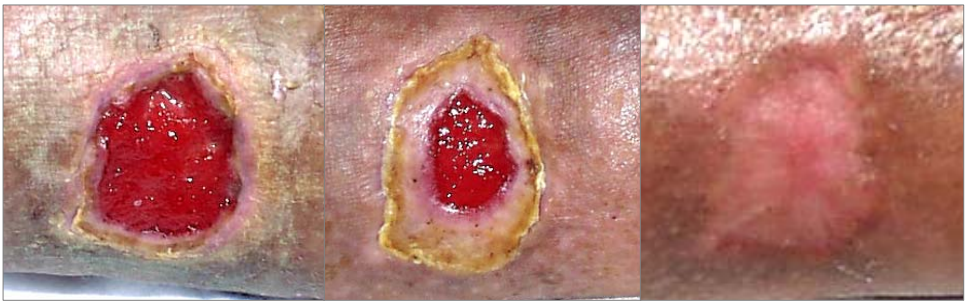
MODELING WOUND PATHOLOGIES

Pathological states of the wound can also be diagrammed.

The main control loop of the wound dynamical system is an "open model", a backbone circuit that allows any and all physiological, pathological, and therapeutic effects to be correctly positioned in the system and inter-related. Here is a sampler of pathological wound states and their representations.

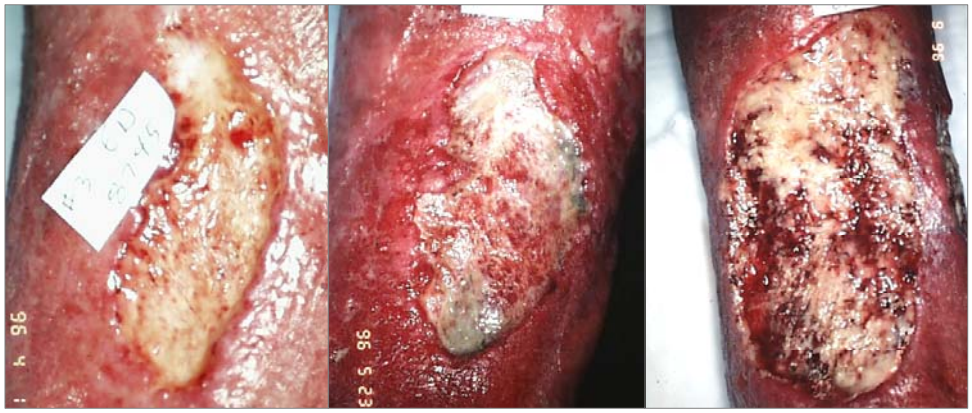
The healthy wound.

This is the ideal wound, healthy, with a one-shot response to injury, a simple "decay" or smooth transition from acutely open back to re-closed.



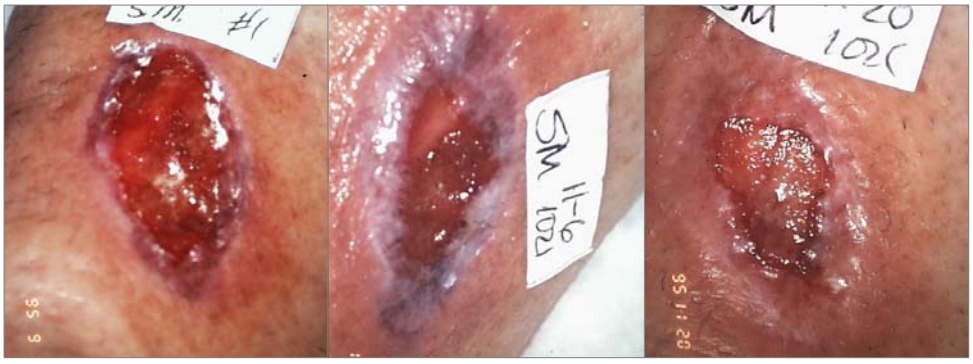
The active divergent wound.

This is the worst wound, acutely pathological and inflamed, actively ulcerating by lysis and necrosis. Dynamically, the control loop has been overwhelmed; the system has saturated in the undesirable state. Bringing the wound back into the operating range of the control loop requires deliberate active therapy.



The chaotic wound.

This is the frustrating wound. From exam to exam, for weeks or months, now a bit better, now a bit worse, the wound has no net change. The control loop orbits in an attractor from which it can escape only with therapies that strongly regulate or drive specific blocks or nodes.



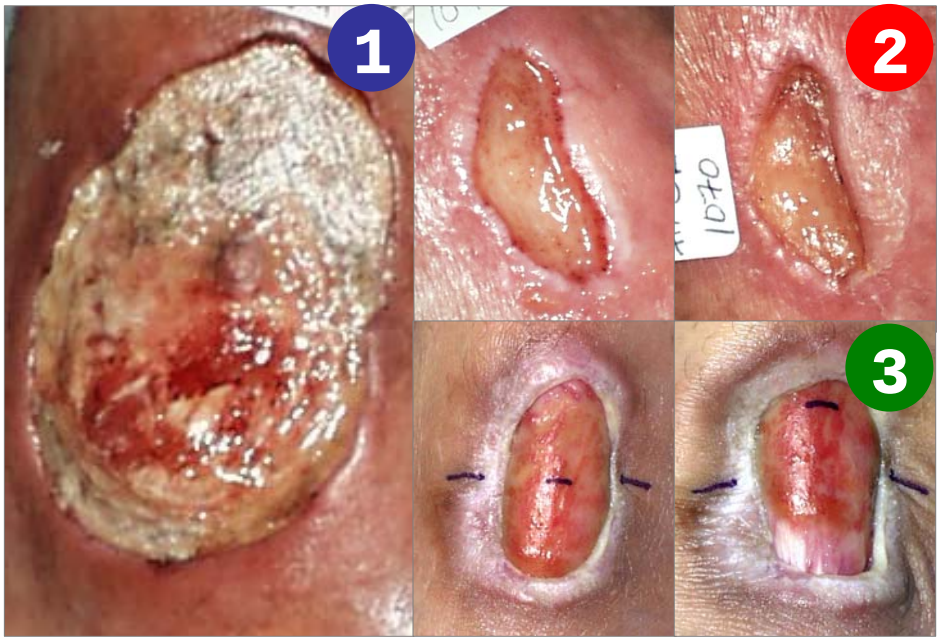
MODELING WOUND PATHOLOGIES

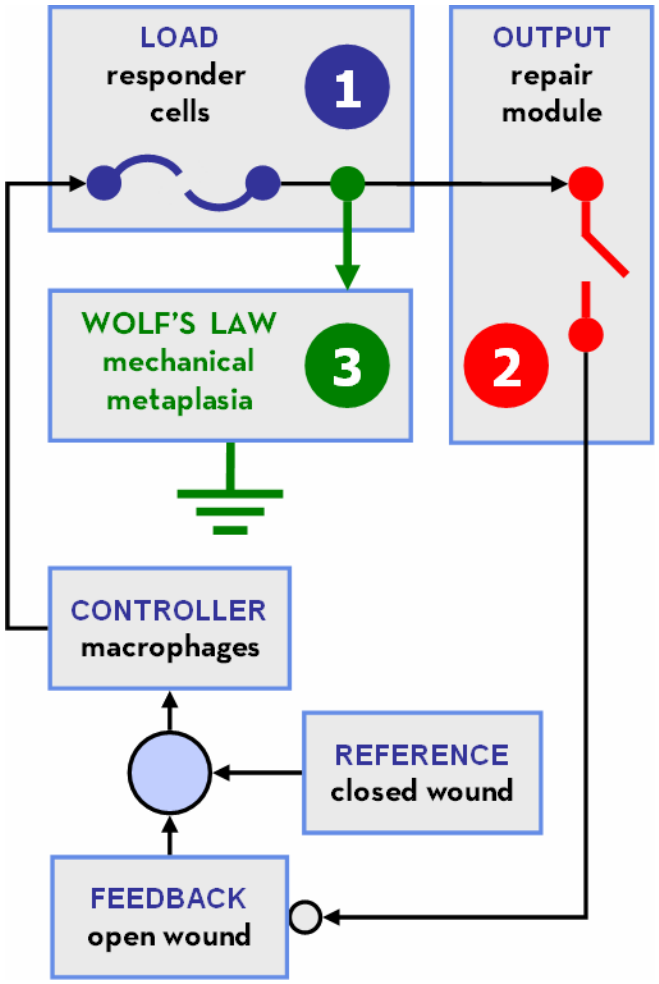
Open circuit wounds.
Some pathologies do not alter loop dynamics, but rather arrest the loop, stopping wound healing until the open circuit is reclosed or restarted.

1 – Radiation wound, 6500 cGy, a dose at which radiation damage to local progenitor cells abolishes proliferation. Responder cells are gone, an open switch, or more correctly, a blown fuse in the loop.

2 – Chemotherapy has a transient effect to diminish responder cell metabolic output, an on-off switch in the output block of the control loop. With cycles of hydroxyurea, this ankle ulcer started and stopped healing, the repair module being cyclically turned on and off.

3 – EDC tendon across ankle. Blue dots show motion. Open tendon surfaces have either normal tenosynovium or else only marginal signs of wound healing. Why? Mesenchyme responds to applied force, differentiating in ways which resist the load (Wolf's Law; compression begets bone, tension begets tendon, etc). Shear induces synovial or serosal metaplasia, a response that assumes that the motion is anatomical (tendons, joints, bursas). Wound healing is simply shut down as the system is shunted off to a physiological "program" of differentiation.



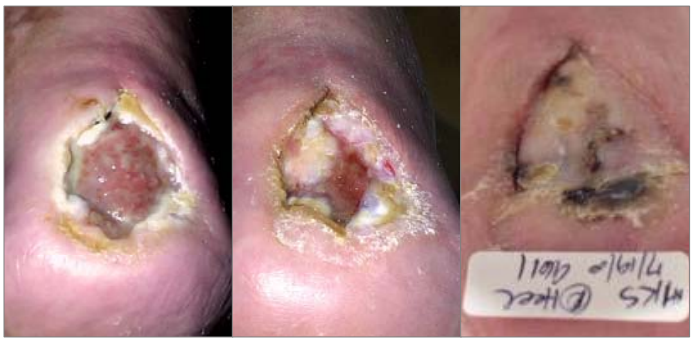


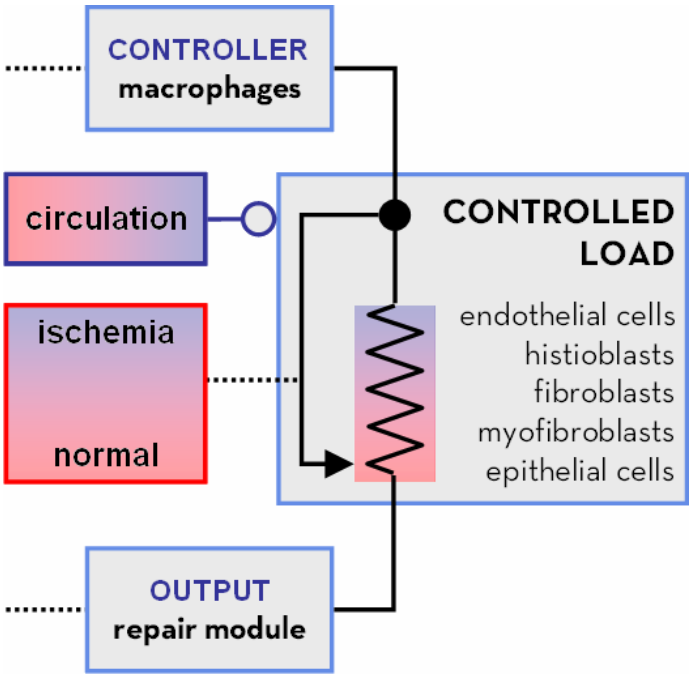
MODELING WOUND PATHOLOGIES

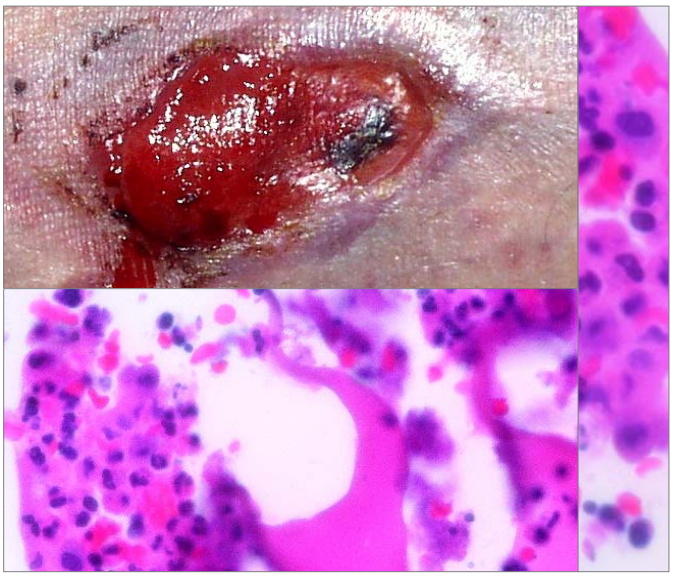
A place for every option and event.
Of the countless factors that influence wounds, two more illustrate how the loop accommodates all.

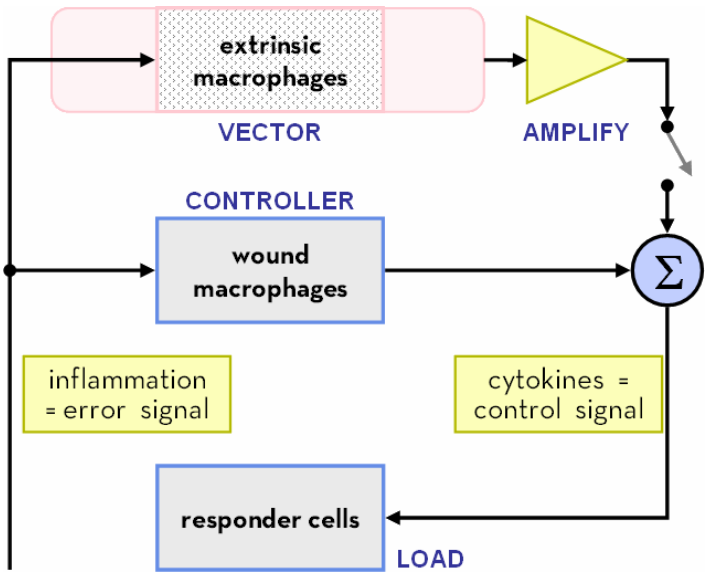
Right – A heel ulcer, with severe arteriosclerosis, healed after a year of topical care. Ischemia suppresses the responder cells. It can be added as a simple inversion or negative latch, but since the wound healing effects of arterial disease are "dose" dependent, ischemia can be modeled as a variable impedance.

Below – Pyogenic granulomas all have a story of prolonged unchanged bandages. A haven for inflammatory cells, the gauze harbors large mononuclear cells (the microscope specimen is of the bandage). The growth factors they issue are a spatial vector which attracts the repair module out of the defect, toward the dressing. They can be added to the loop as an amplified element parallel to the normal macrophages.









Key Points and Summary

The wound is a control system. Healthy wounds start and stop healing at the correct time, and they produce the correct result. This is because they are a controlled system, meaning a self-targeting system with feedback. As with any non-linear machine, especially a complex machine with hundreds of interacting elements, it is not possible to understand the system as a whole, or its complex behaviors, by using classic bioscience experiments which study only one-versus-another parameter.

The wound module and the main control loop. The intrinsic machinery of wound healing is the wound module of post-inflammatory proliferative repair. It is a collection of cellular and chemical elements with a set of operational interactions and dynamics. Its elements and operations are the core or kernel of the wound healing control loop.

Wound dynamics and controlled responses. Healthy wounds respond to acute incidental injury, single perturbation, by a direct non-oscillatory transition back to the reference state of being closed. Other control system responses can occur, depending on cause and severity of the applied injury, and the health of the wound module elements. Most chronic wounds exhibit chaotic behavior, orbiting an attractor that, while clinically undesirable, is dynamically stable and hard to change.

Modeling healthy and pathological wound states. The wound control loop is an open kernel, a core model permitting any and all other elements and interactions to be added. It explains physiological wound behaviors, pathological wound states, and responses to treatment. It identifies points in the machine where errors occur, and where therapy might be introduced.

Wound Physiology in the Century of the System

In human engineered systems, machines are designed to have a particular stability or output. For example, it is important to understand how a signal or state is transformed through a control block (transfer function), and it is important to design a system with correct feedback to avoid oscillations. In support of these goals, there are robust math and engineering methods, such as second order differentials, convolutions, and LaPlace transforms, which permit the exact design and precise numerical specification of a planned machine and its activities.

These practices also apply to The Wound, in principle. However, we have too little knowledge of wound physics to have precise engineering specs and numerical characterizations of the wound machine. Nobody studies the wound that way, but we now understand that complex biological systems must be studied as machines, not just as a collection of isolated one-on-one elements. This is mandatory for the wound, if its timewise behavior and response to injury and therapy are to be understood, especially in the impaired wound where the road to the desired result is not so easily traveled.

The purpose of this paper is to raise awareness that the wound is a complex system, and that it must be approached that way This is the century of The System, when the dozens or thousands of cells and chemical which participate in a system will be understood not through the linear chemistry and physiology of yesteryear (which remain vitally important to analyze individual system components), but through system or machine-level analysis using the principles of non-linear dynamics and complex systems.

The wound is a complex machine. It must be studied that way.
The MAIN CONTROL LOOP of the wound module is the foundation system.

END