Having a swell time:

Nonlinear dynamics of sepsis and inflammation

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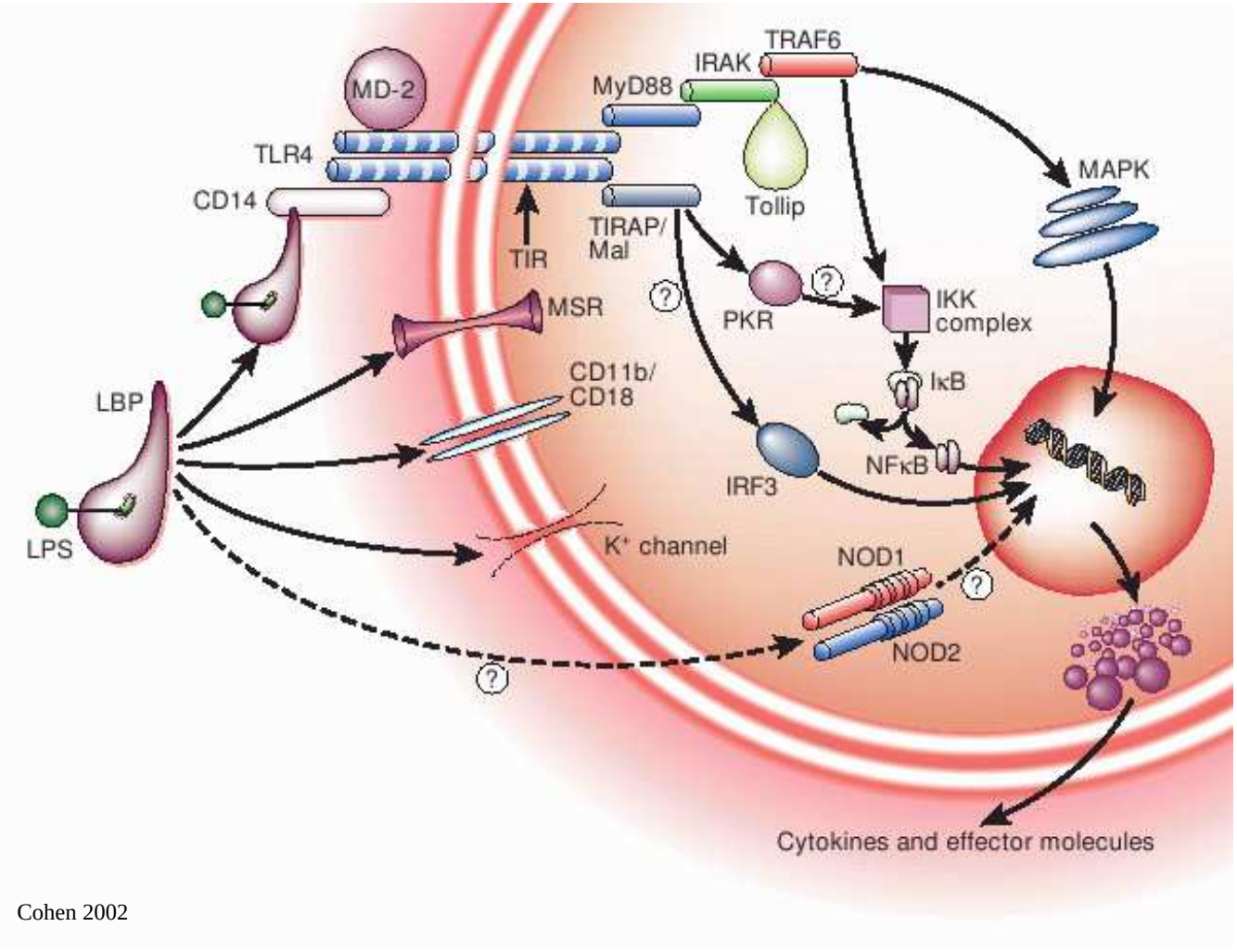
First the collaborators!

- Angela Reynolds (PhD student, VCU)
- Gilles Clermont (Critical care medicine)
- Jonathan Rubin (Pitt,math)
- Yoram Vodovotz (Surgery)
- Judy Day, Carson Chow, David Hackham and others

Sepsis

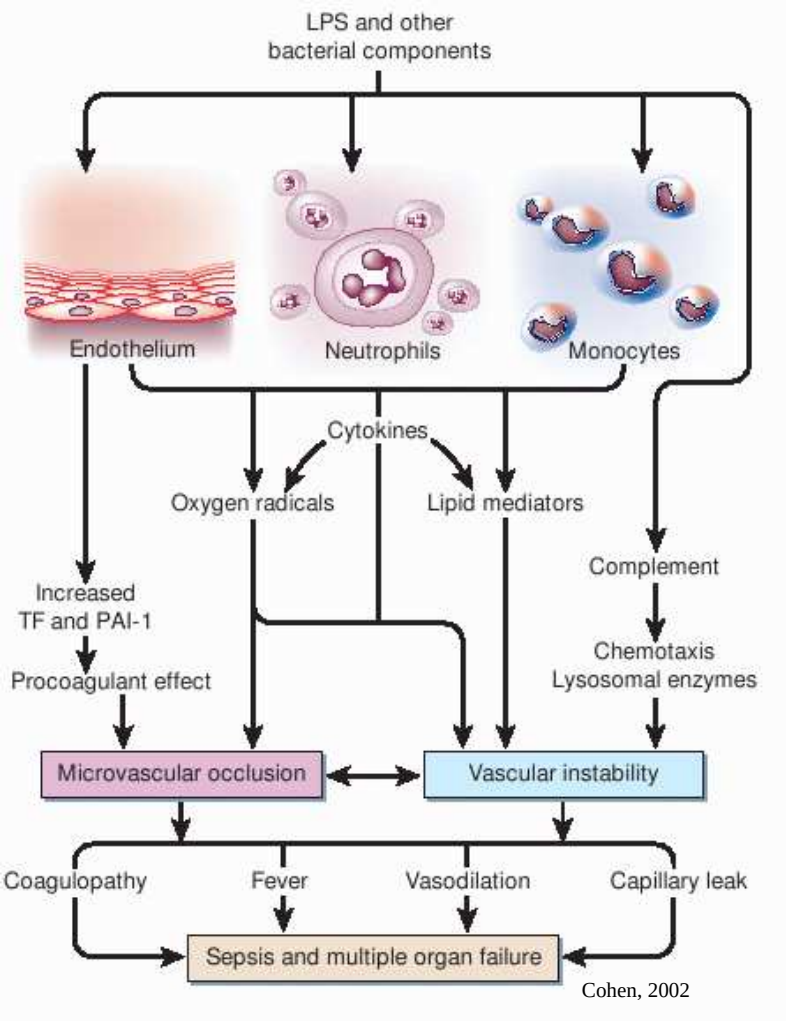
- Sepsis is a complex clinical syndrome that results from a damaging response to some form of insult such as trauma or infection.
- It occurs when the original reaction is amplified and poorly regulated.
- 3 cases per 1000 patients in North America resulting in 780,000 cases annually (Cohen, 2002)
- Mortality of about 30% , 40% for the elderly, and 50% for those with septic shock (op cit)
- Commonest sites are the lungs, abdominal cavity, urinary tract, and blood stream
- Key factors are the innate immune response and inflammation

Initiation of Sepsis



Cohen 2002

Pathological path of sepsis

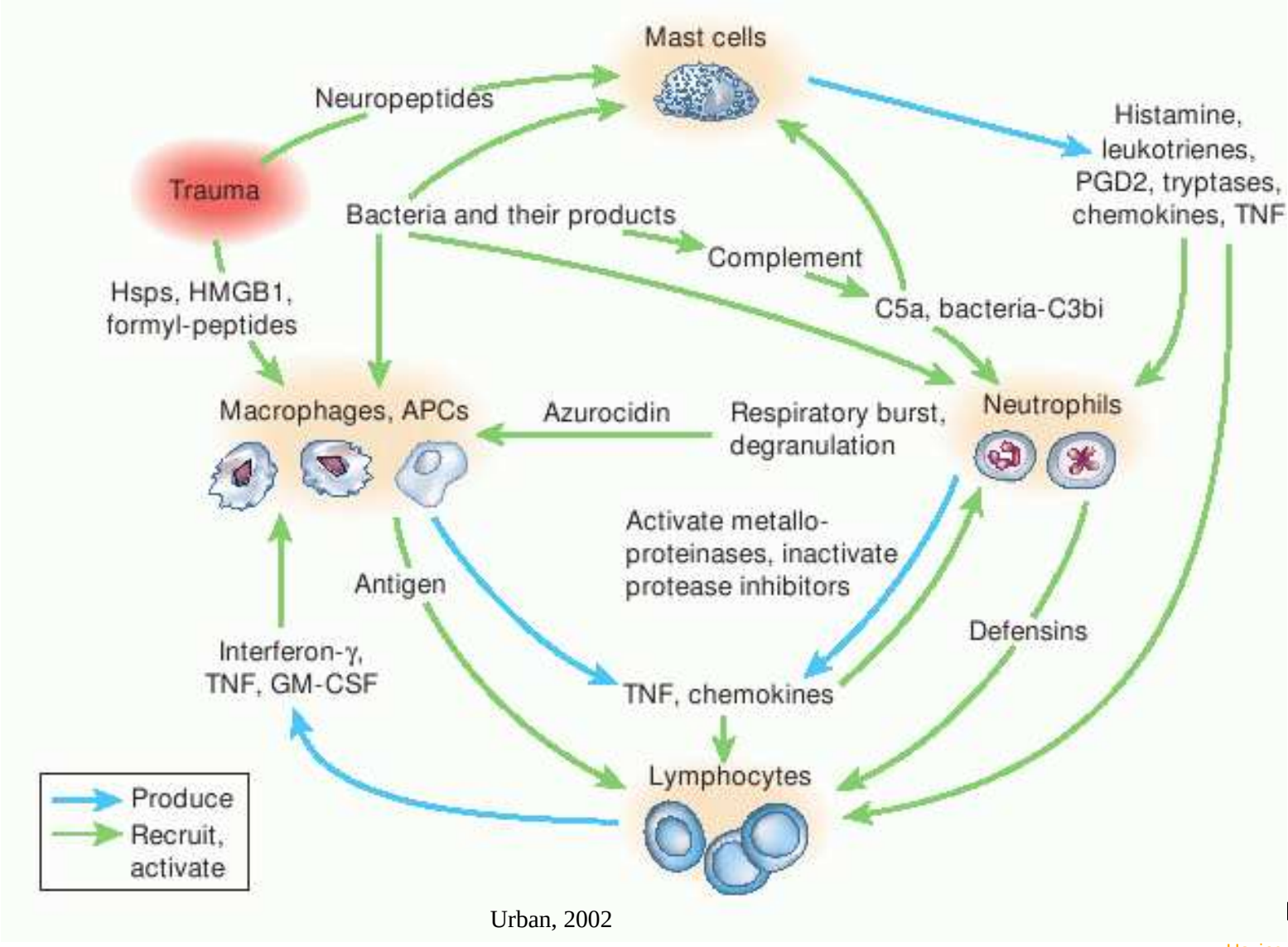


Cohen, 2002

Inflammation

- Inflammation is a complex process that involves multiple soluble factors and cell types which arises as a response to trauma, infection, toxic injury, or autoimmune reactions.
- The goal of the response is to clear pathogens and initiate the healing process.
- Inflammation is carefully controlled by the timely interactions of pro- and anti-inflammatory signals.
- Disruption of the timing and balance of these factors can lead to destruction of tissue and ultimately in a clinical setting to sepsi.
- *The non-inflammatory state does not arise passively from an absence of inflammatory stimuli; rather, maintenance of health requires the positive actions of specific gene products to suppress reactions to potentially inflammatory stimuli that do not warrant a full response.* **Urban, 2002**

The inflammatory loop



Urban, 2002

Biology is complex

- Many biological systems are regulated by multiple feedback pathways, amplification of signals, delayed suppression and multiple possible outcomes and states.
- Cell division; mitosis & meiosis; apoptosis; calcium-induced calcium release
- Neural/cardiac excitability; propagation; rhythms; short-term memories
- Cellular physiology: peristaltic waves, concentration of urine, insulin secretion

Why do we need theory?

Intuition and concepts constitute, therefore, the elements of all our knowledge, so that neither concepts without an intuition in some way corresponding to them, nor intuition without concepts, can yield knowledge... Thoughts without content are empty, intuitions without concepts are blind...Only through their union can knowledge arise.

-I. Kant, *Critique of pure reason*

Mathematical models

- Boxes and arrows suggest mechanisms but when there are many pathways, the outcomes are not always obvious.
- For example,when should the system switch from killing to healing? How does this occur? E.g, early on, interferon-γ induces cytokine production in macrophages but later suppresses it.
- The previously mentioned areas of biology and physiology have utilized many ideas from nonlinear dynamics, the study of how systems interact and evolve over time and space
- Creation of a concrete mathemtical model (in the form of, say, differential equations) allows one to exploit the tools developed in nonlinear dynamics such as stability, oscillatory phenomena, bifurcation, etc.

Bistability

- Systems with net positive feedback can be expected to exhibit multiple stable states
- Neuroscience
  - up and down stattes
  - working memory
- Cell biology
  - Apoptosis
  - Portions of the mitotic cycle (J. Tyson)

Excitability

- Positive + negative feedback results in excitability
  - Threshold
  - Amplification
  - Refractory period
- Calcium waves
- Action potentials
- Immume response to insult

Oscillations

- Onset from excitable systems in only a few ways
  - Hopf bifurcation
  - SNIC
- Ubiquitous in physiology: heart, respiration, motor patterns, smooth muscle
- Neural oscillators – cognition??
- Pathologies – epilepsy, Parkinsonian tremor, etc
- Periodic fevers?

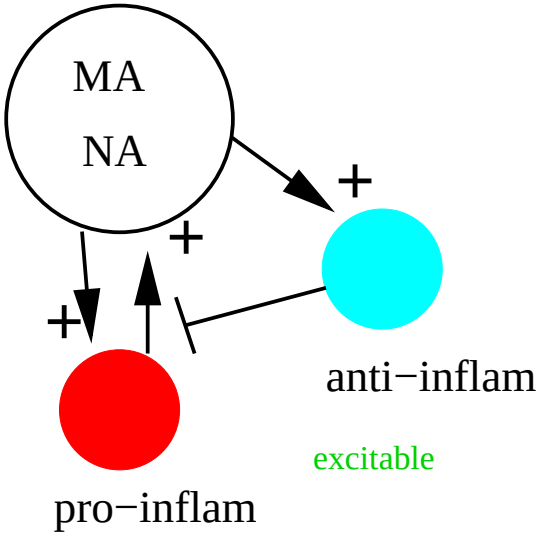
Spatial dynamics

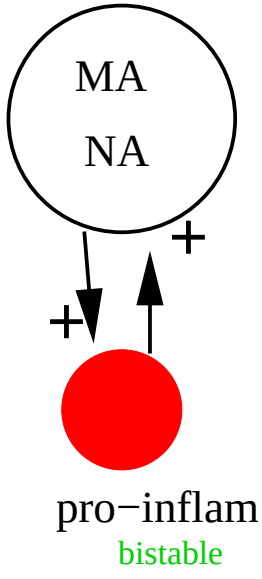
- Patterns are ubiquitous at all levels
- Waves, complex patterns, localiszed patterns
- Are there analogies in the inflammatory response?
  - erythema gyratum repens
  - erythema migrans (Lyme rash)
  - geography tongue
  - Measles, chickenpox, etc ?

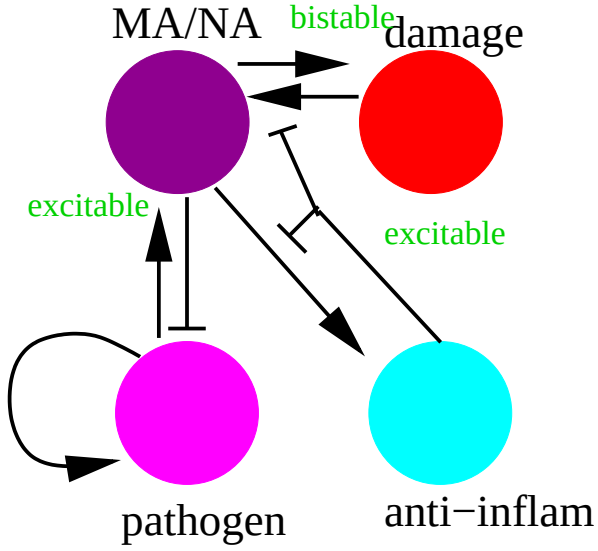
In the remainder of this talk, I will discuss some of the examples from our group that apply the methods of ND to inflammation and sepsis. In the lab, you will get to play with some of these models.

- Simple models of the inflammatory response
- Necrotizing enterocolitis
- Lung inflammation
- Periodic fevers
- Rashes

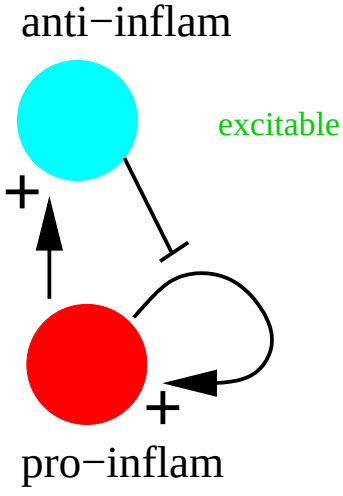
Simple models

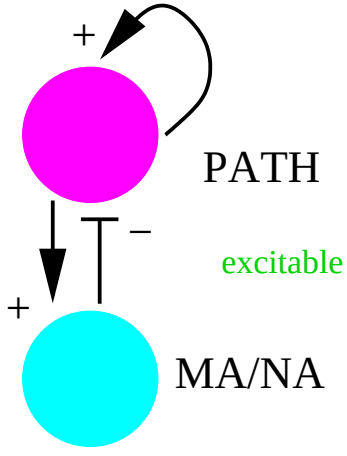






Reynolds et al





Pathogens vs macrophages I.

Let's begin with a very simple part of the loop.

- Pathogens grow logistically to a carrying capacity:

$$\frac{dp}{dt} = p(1 - p/p_{max})$$

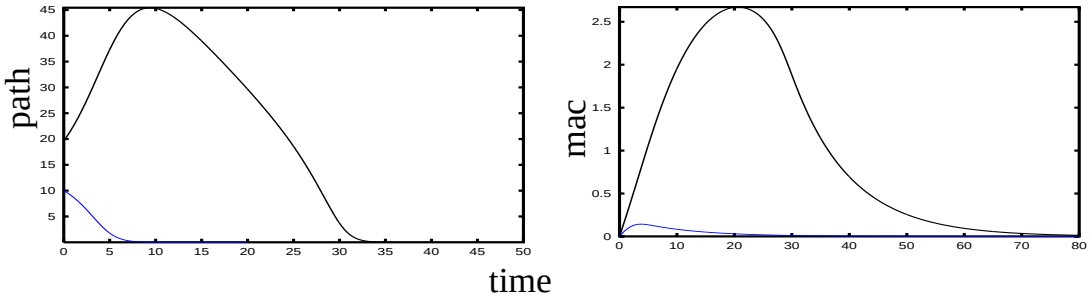
- There is an innate defense that can be overwhelmed by too much infection which kills the pathogens

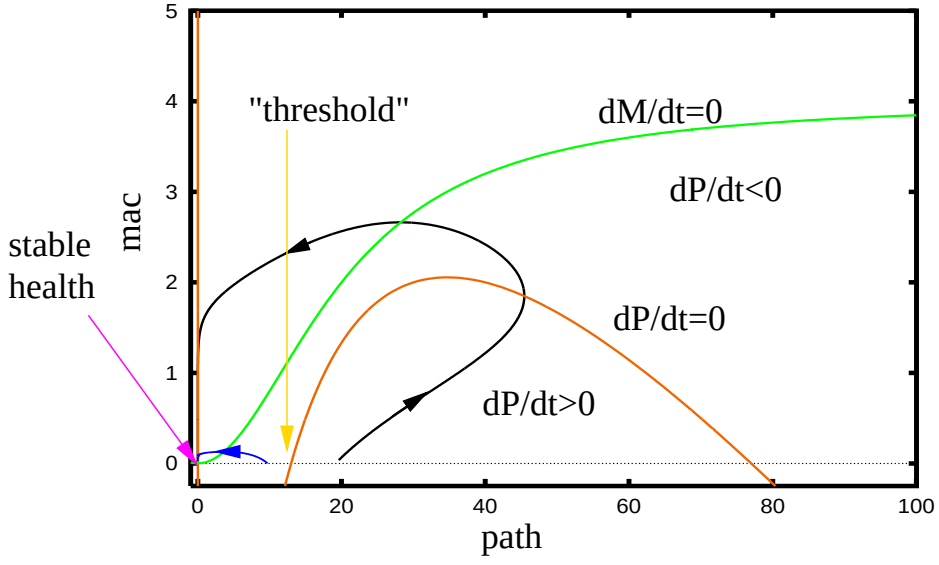
$$\frac{dp}{dt} = p(1 - p/p_{max}) - a\frac{p}{p+b}$$

- Pathogens call in more macrophages which kill the pathogens

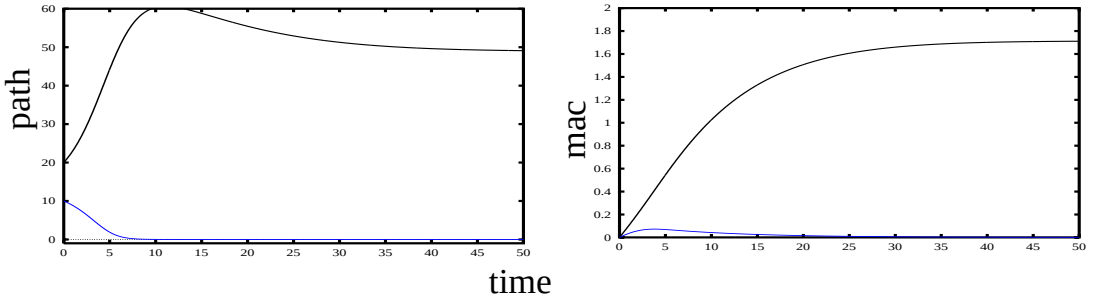
$$\begin{aligned} \frac{dp}{dt} &= p(1 - p/p_{max}) - a\frac{p}{p+b} - km_a p \\ \frac{m_a}{dt} &= \frac{m_0 p}{p_0 + p} - \frac{m_a}{\tau} \end{aligned}$$

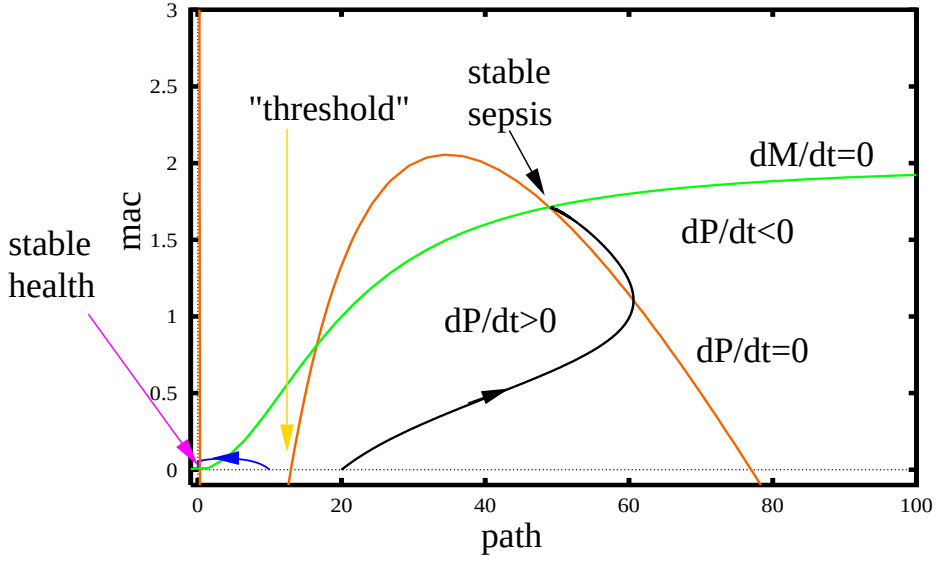
Health is stable/resolved



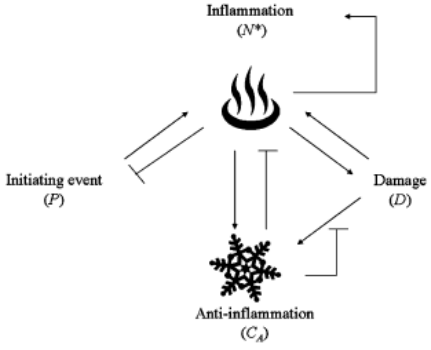


Health is stable/weakened response





A more complex model



- Pathogens induce neutrophils
- Neutrophils cause “collateral damage” releasing more cytokine
- Pro-/anti-inflammatory cytokines are released
- Multiple feedback loops

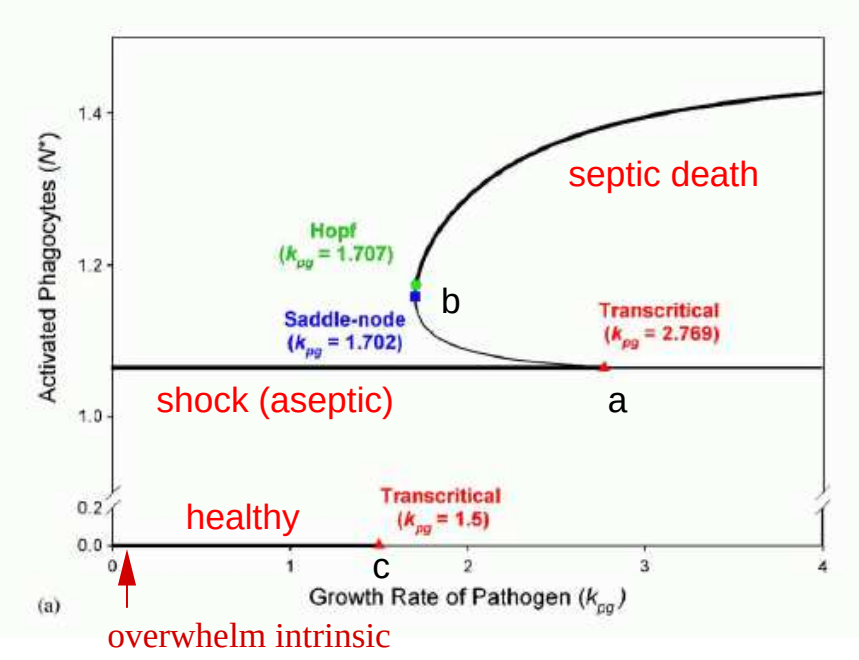
Main players

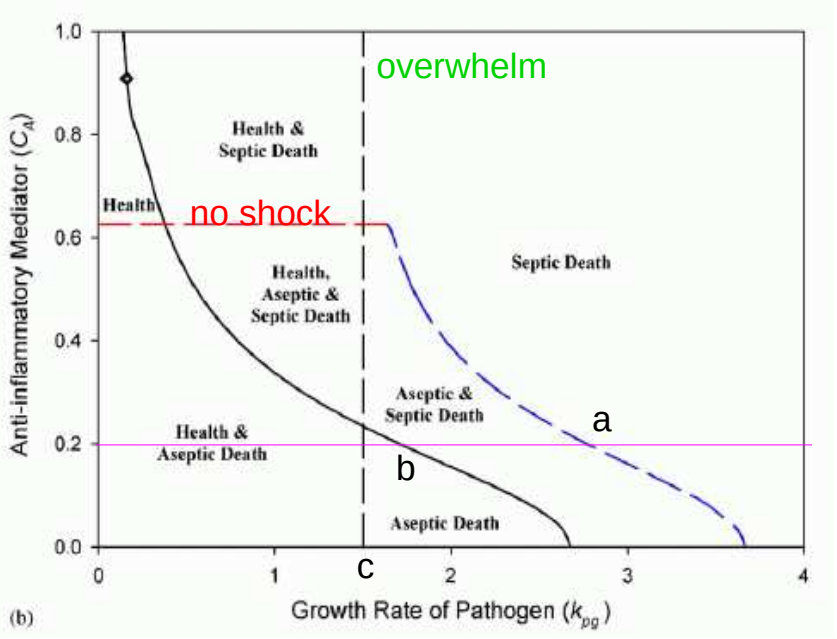
- Local immune response - macrophages
- Neutrophils – called in by the immune response
- Cell damage releases free radicals
- Cytokines further activating neutrophils
- . . . as well as inhibitors which cool off

Key component:multistability

- Small infections kept back by local immune system;
- Larger insults require neutrophils
- . . . which themselves cause collateral damage
- . . . bringing in more neutrophils
- How do you balance this?

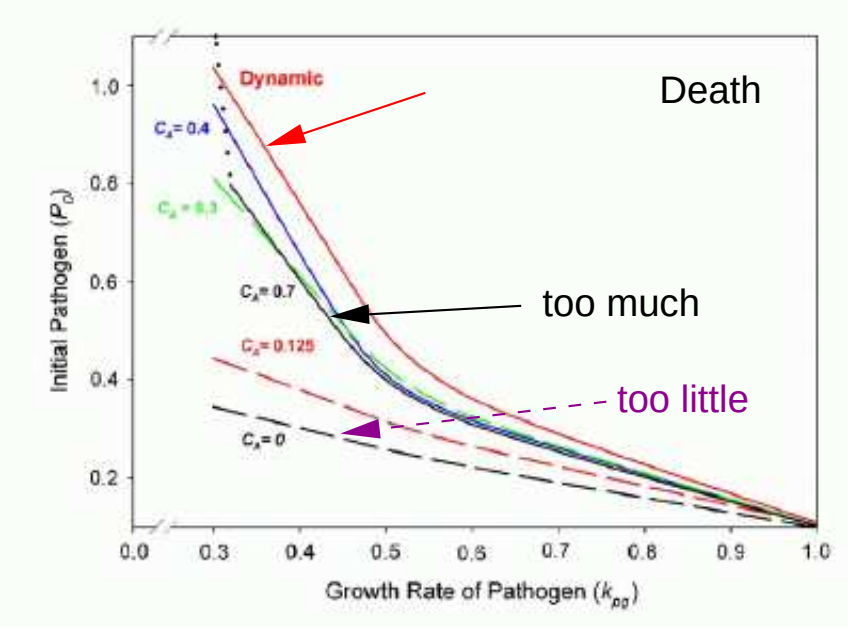
Constant inhibition

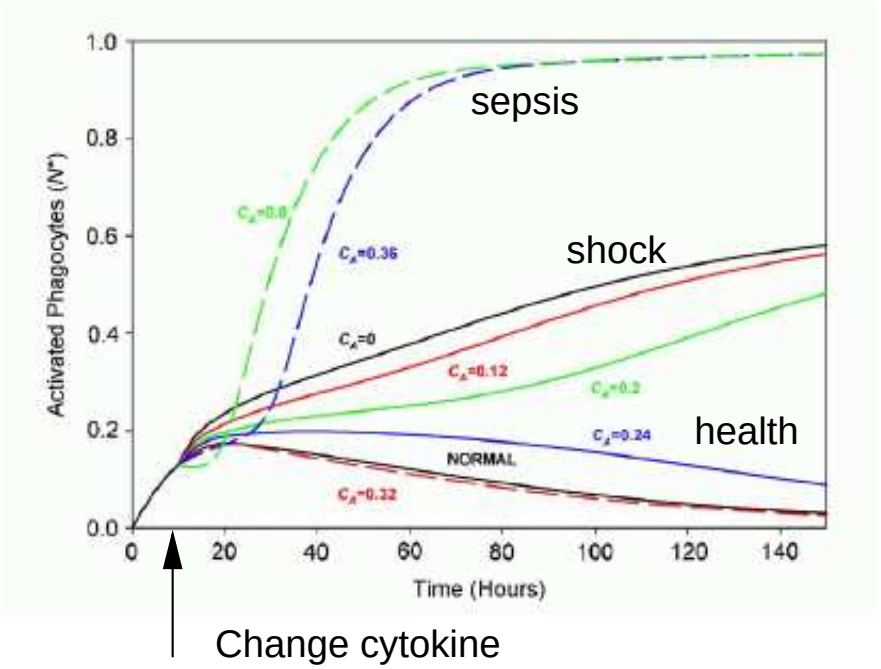




- Too little C_A and there is strong risk of shock
- Too much and the infection overwhelms
- Suggests danger in anti-inflammatory therapy

Dynamic inhibition confers stability



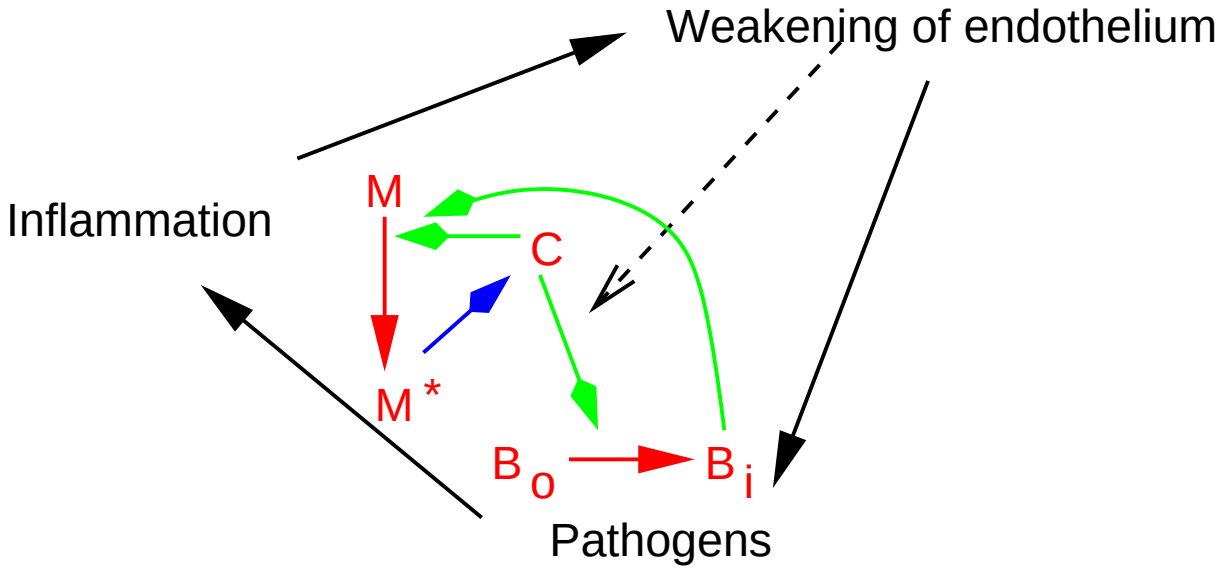


- Allowing CA to be dynamic allows a broader range of health
- Caution when applying CA therapy

Necrotizing enterocolitis

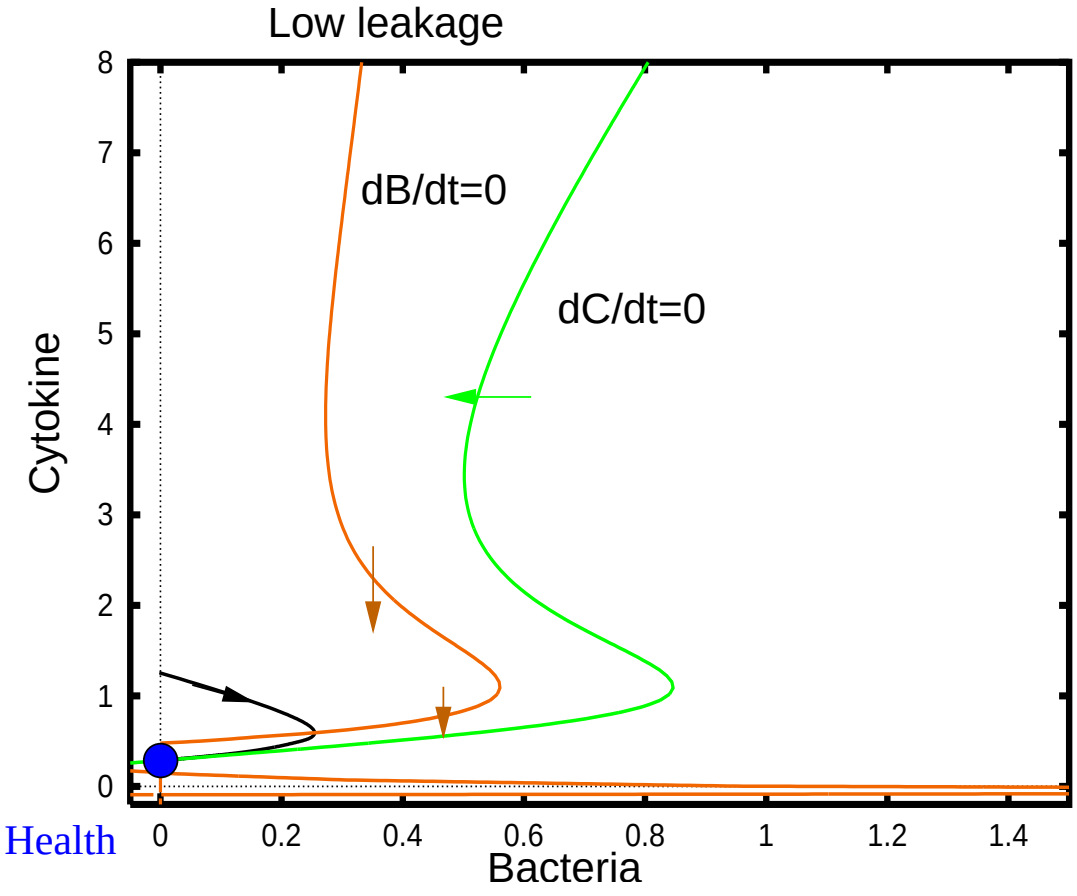
- Necrotizing enterocolitis (NEC) is the most common and lethal disease that affects the gastrointestinal (GI) tract of the premature infant.
- Severe version result in destruction of the epithelial lining, bowel necrosis, peritonitis accompanied by bacterial invasion and sepsis
- Overall mortality for NEC ranges from 10% to 50%
- Etiology of NEC remains undefined.

A simple model for NEC

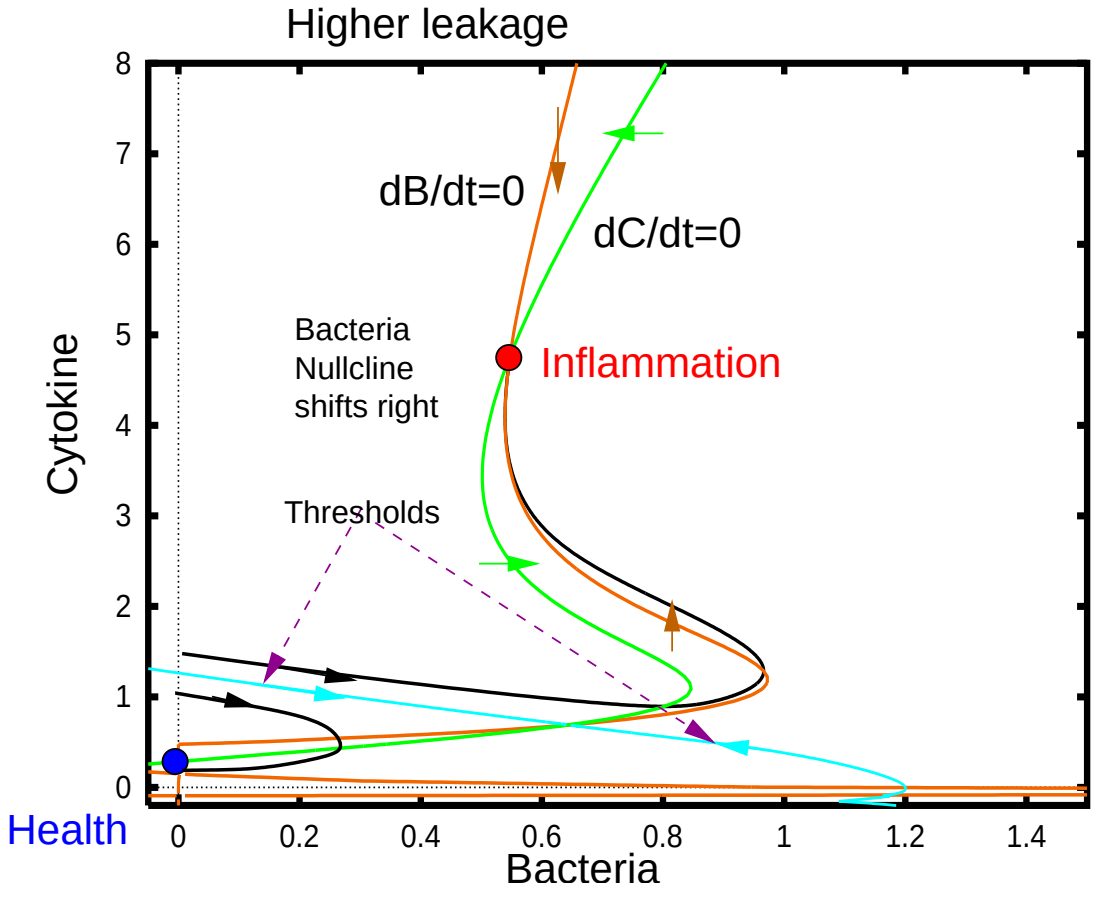


Neutrophils N become activated N^* via proinflammatory molecules C or bacterial LPS, B_i inside the epithelium. C cause damage to the epithelium allowing luminal bacteria, B_o to leak through. N^* release more C.

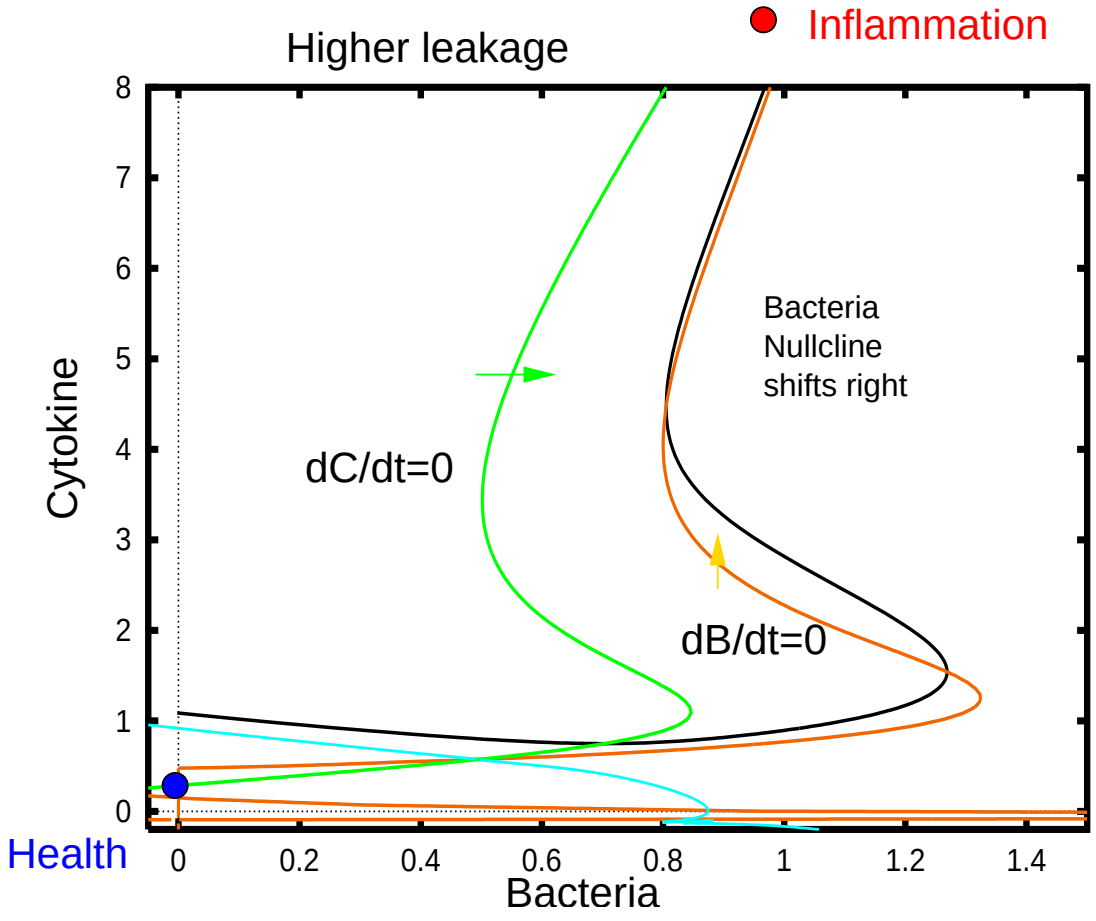
Normal low leakage



Pathological leakage



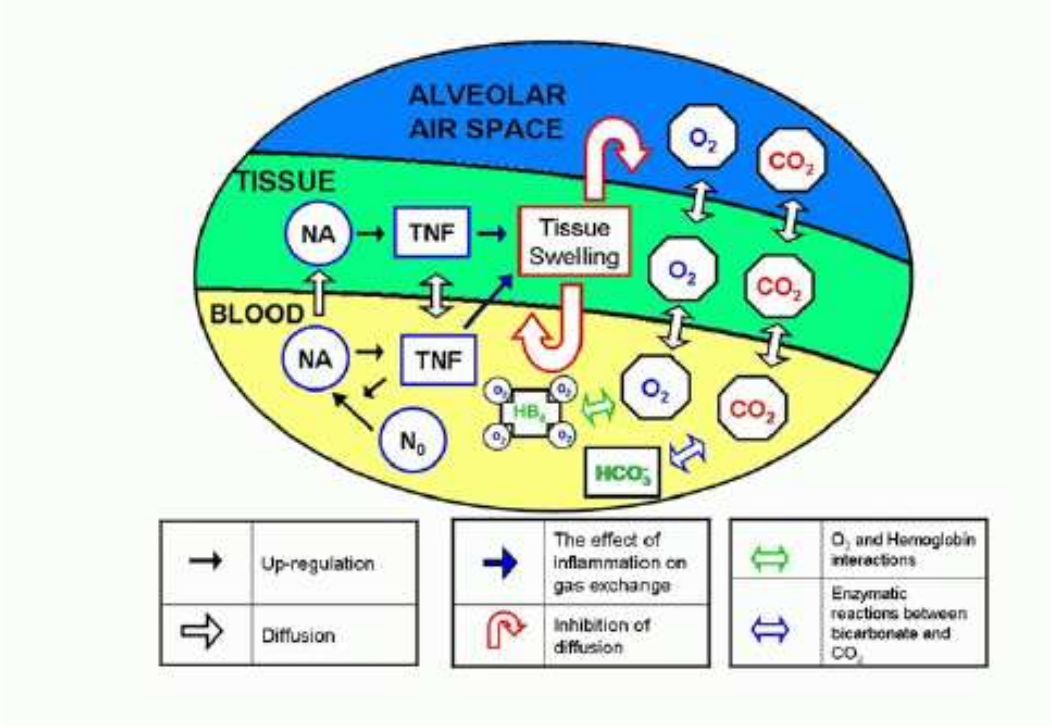
Even higher leakage

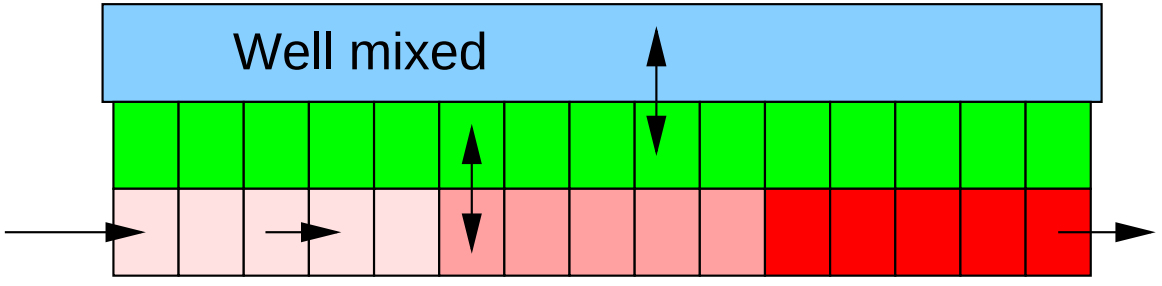


Inflammation and the lung

- Acute lung inflammation can be triggered by chemics, infectious or traumatic stimuli.
- Often requires mechanical ventilation
- Most frequent manifestation of multisystem organ dysfunction
- A leading cause of death in thr ICU

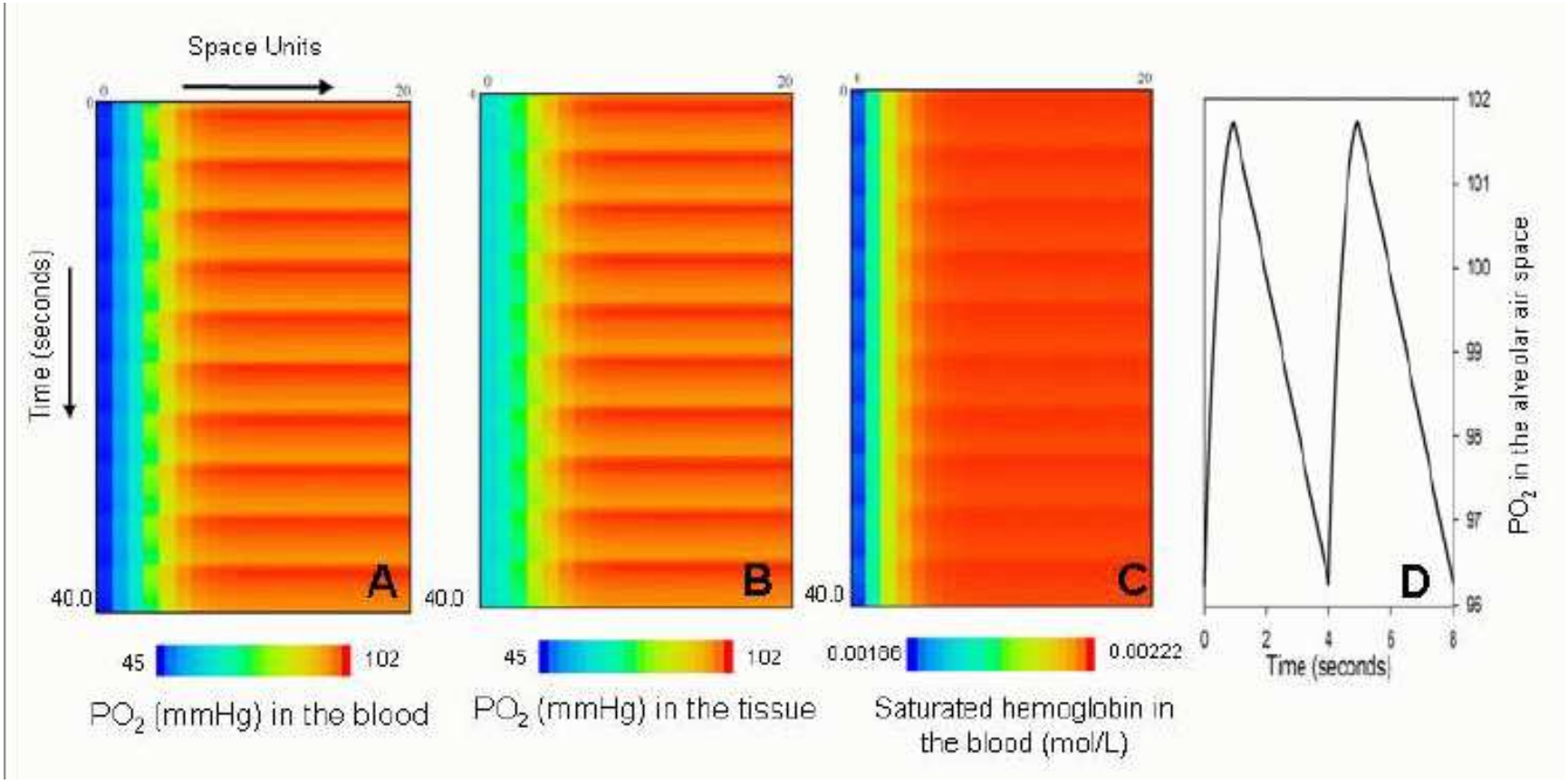
Single Alveolar unit





Single alveolar unit

Normal unit


Space Units
Time (seconds)
40.0
A
B
C
D
45
102
PO_2 (mmHg) in the blood
PO_2 (mmHg) in the tissue
0.00186
0.00222
Saturated hemoglobin in the blood (mol/L)
PO_2 in the alveolar air space
Time (seconds)

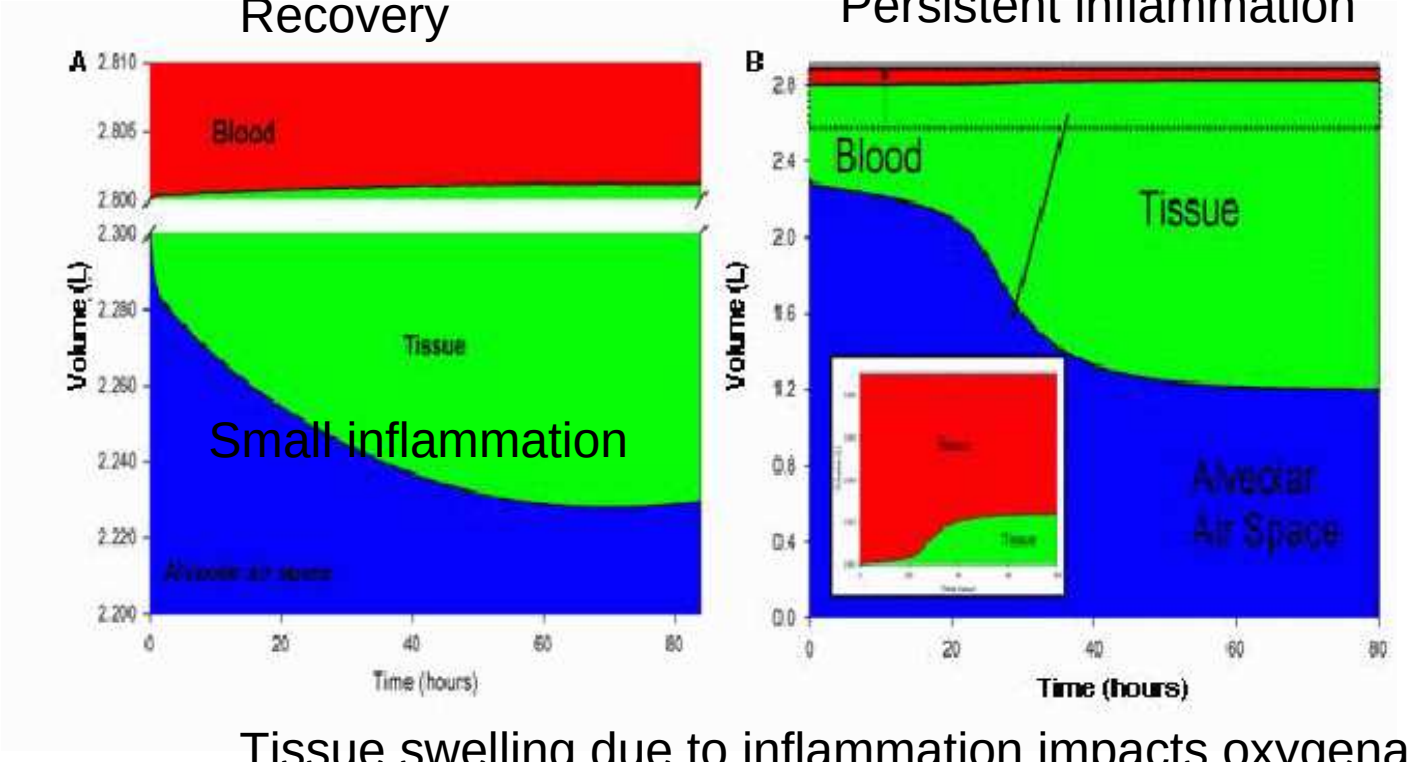
Inflammation of alveolus

Low levels of TNF

Recovery

High levels of TNF

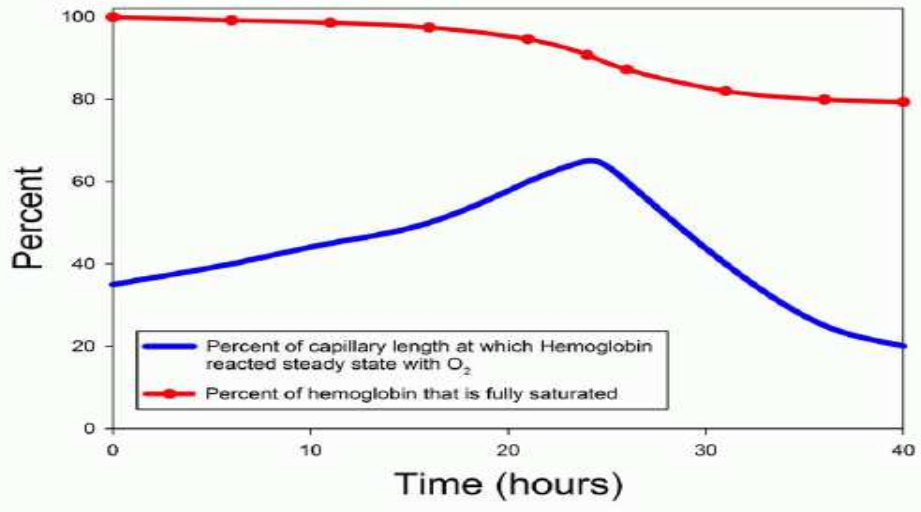
Persistent inflammation



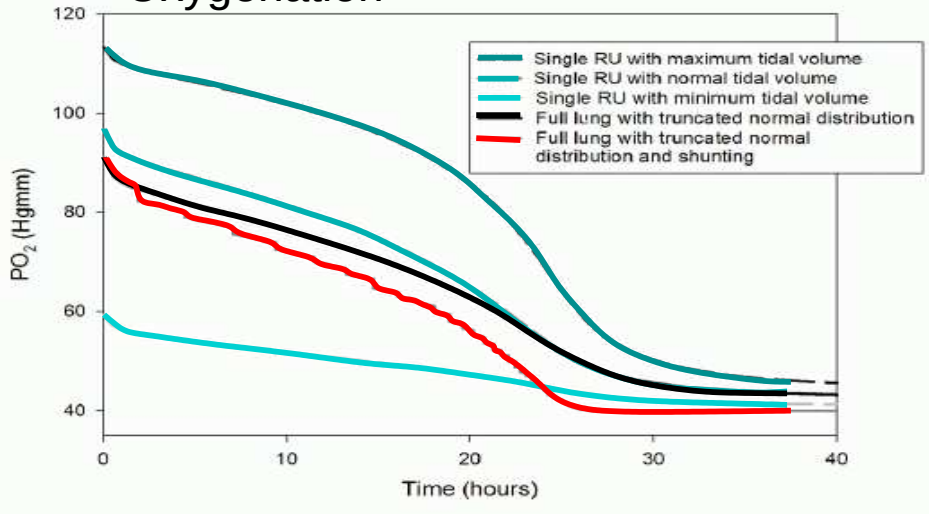
Tissue swelling due to inflammation impacts oxygenation fostering collapse (shunting) of alveolus

Quantification

Saturation of hemoglobin



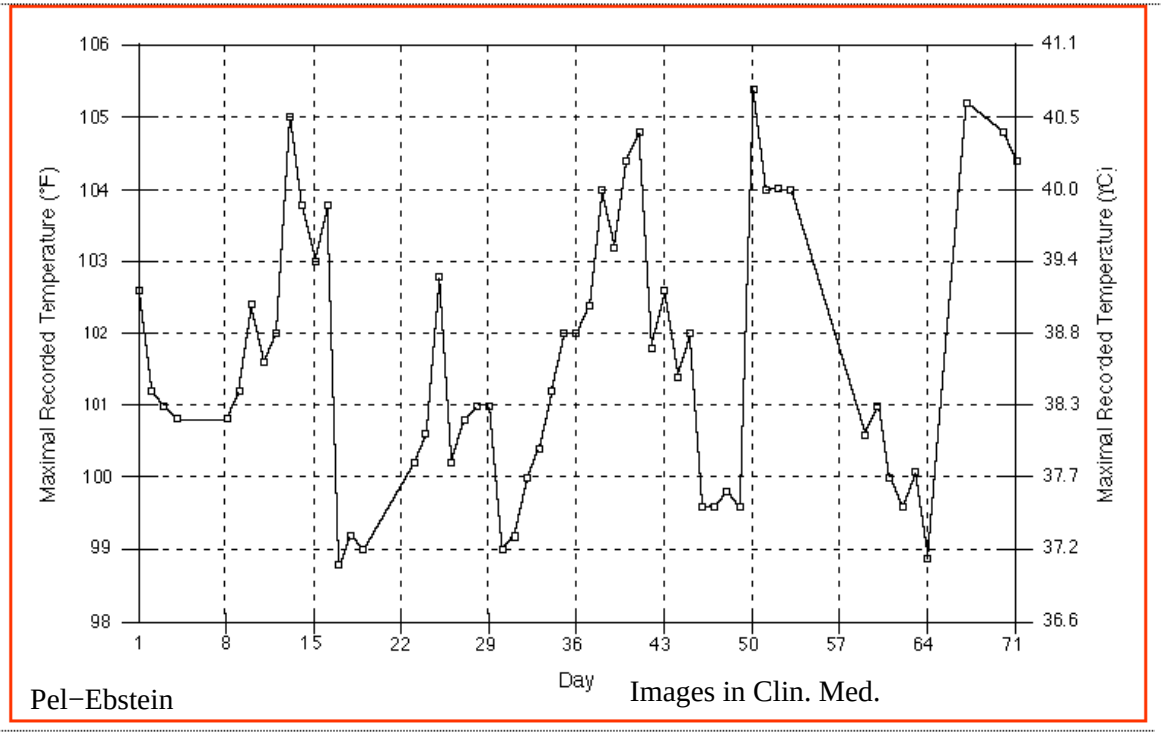
Oxygenation



Recurrent inflammation

- Tonsillitis,otitis media, herpes
- Auto-inflammatory disease (irritable bowel syndrome, lupus, etc)
- Periodic fevers: Familial Mediterranean Fever (FMF), Hyper IgD Disorder, TNF receptor associated periodic fever syndrome (TRAPS), PFAPA (children), Pel-Ebstein
- Relapsing fevers

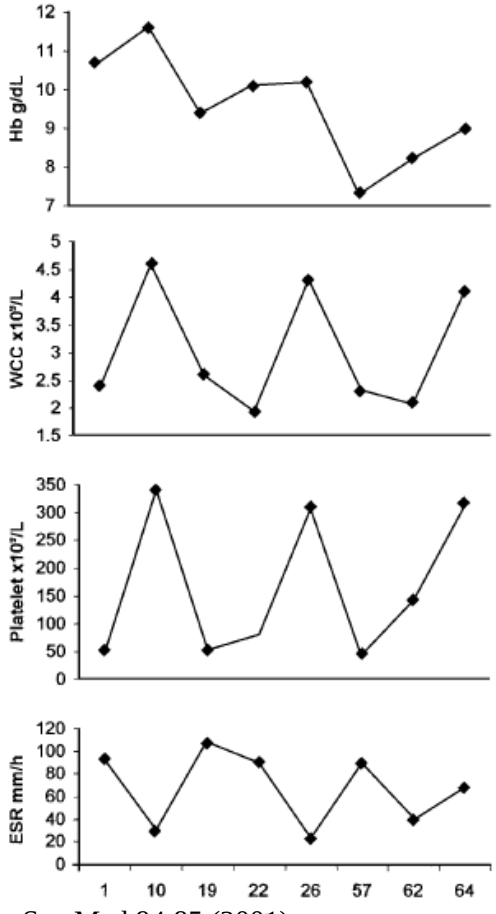
Examples



Pel−Ebstein

Images in Clin. Med.

Pel−Ebstein



J. Roy Soc Med 94:85 (2001)

Woman on antibiotics

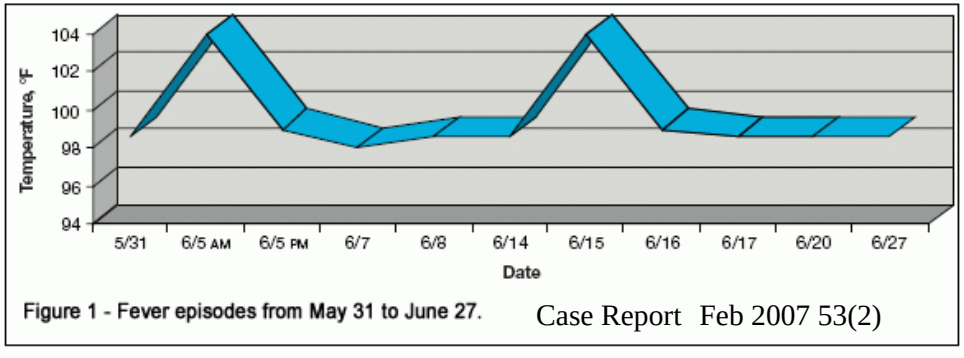


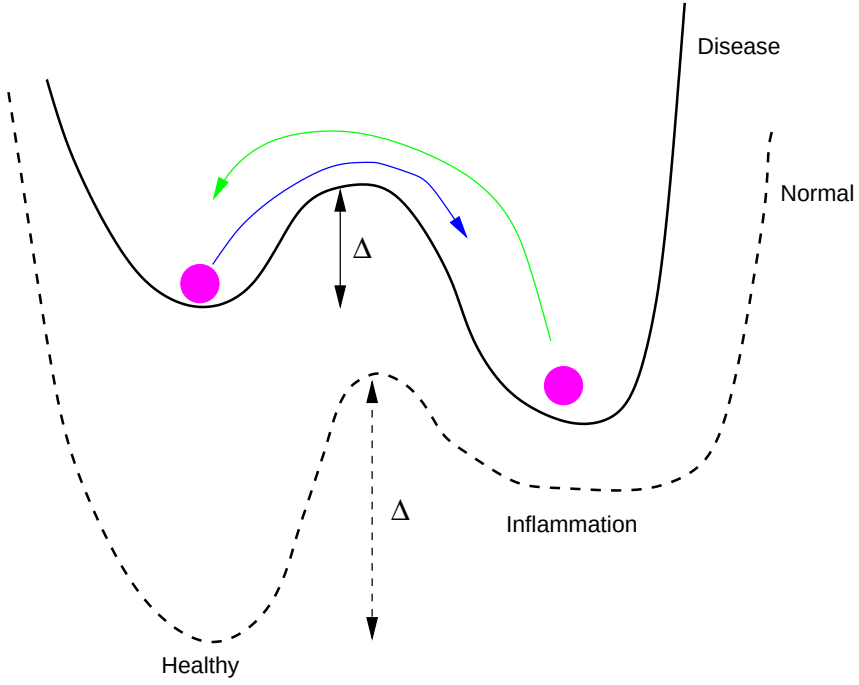
Figure 1 - Fever episodes from May 31 to June 27.

Case Report Feb 2007 53(2)

General mechanisms for recurrence

- Noisy bistability (most irregular)
- Noisy excitability (can be quite regular)
- Periodicity (most regular)

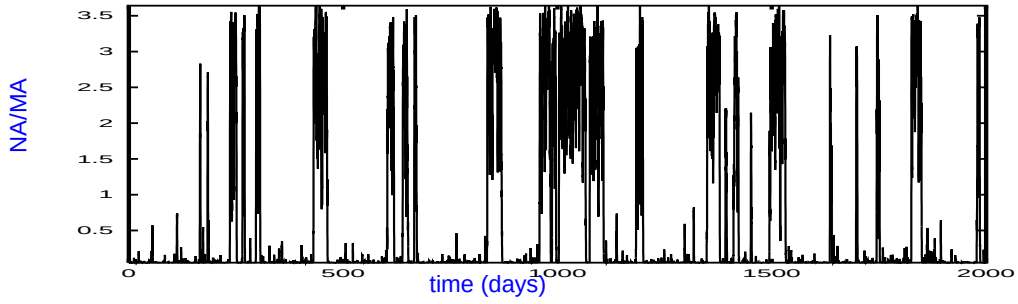
Noisy bistability

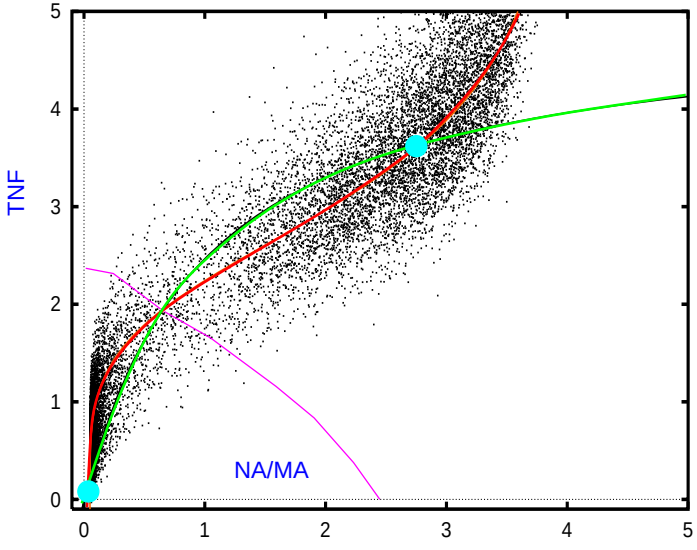


The expected time to spontaneously jump to the inflamed state is

$$T \approx K \exp\left(\frac{\Delta}{D}\right)$$

Model example





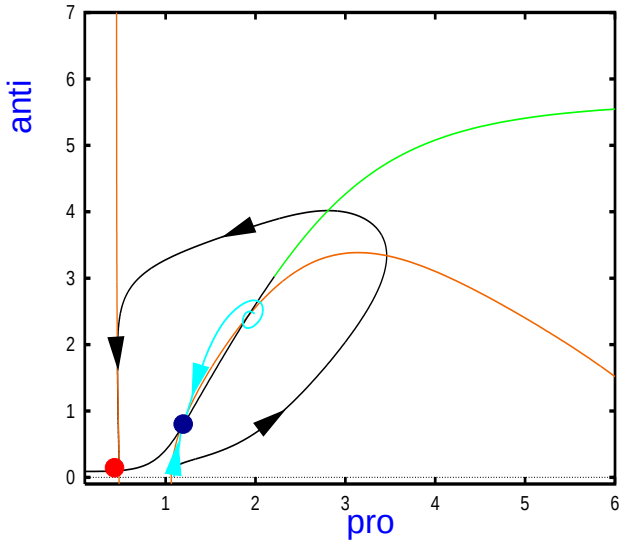
Irregular behavior; recurrent but not very periodic.

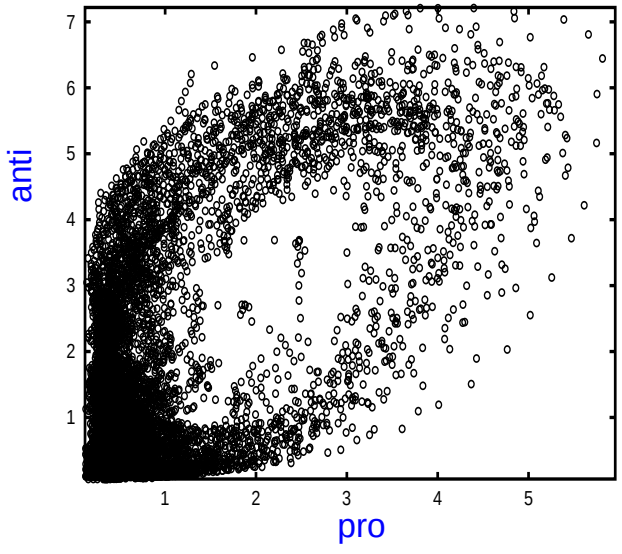
In fact, a nearly Poisson distribution.

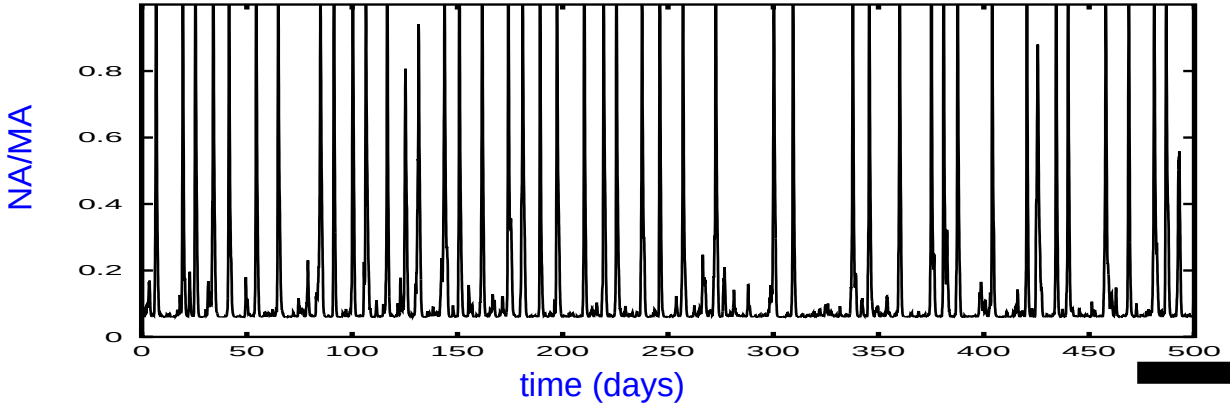
Excitable systems

- Excitability is a natural consequence of the inflammatory response
- Amplification (in the form of exponential pathogen growth or effects of inflammatory cytokines); must cross threshold (e.g. in bistable system or overcome background immune response)
- Recovery and refractoriness; anti-inflammatory cytokines quash response
- Ideal conditions:
  - “inhibition” is feedback
  - “inhibition” is slower and strong
  - Window of opportunity

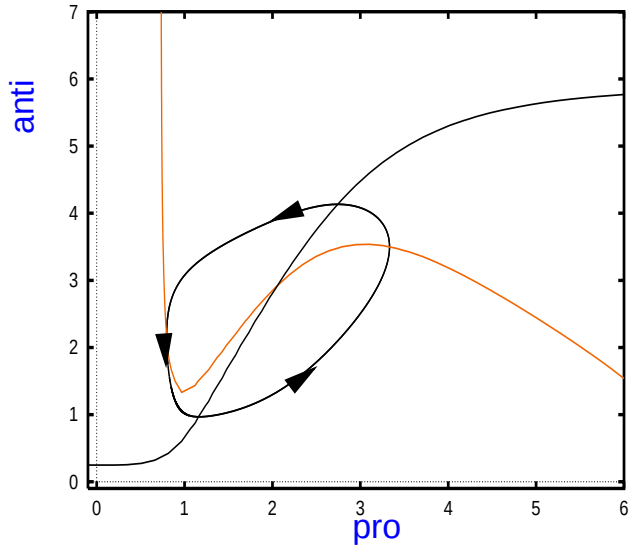
Noisy excitability /periodicity

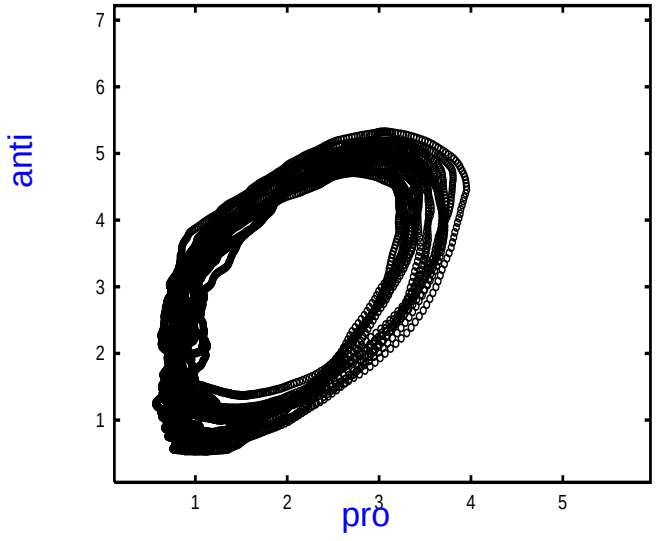


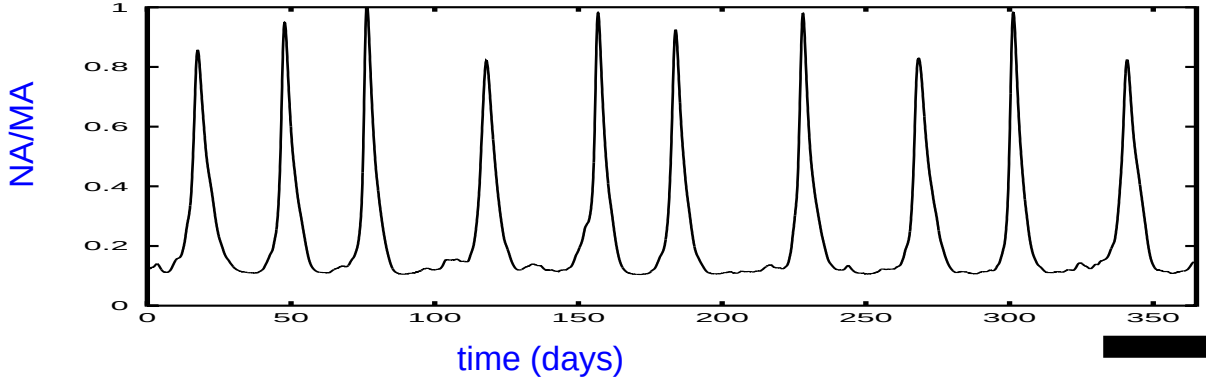




True periodicity

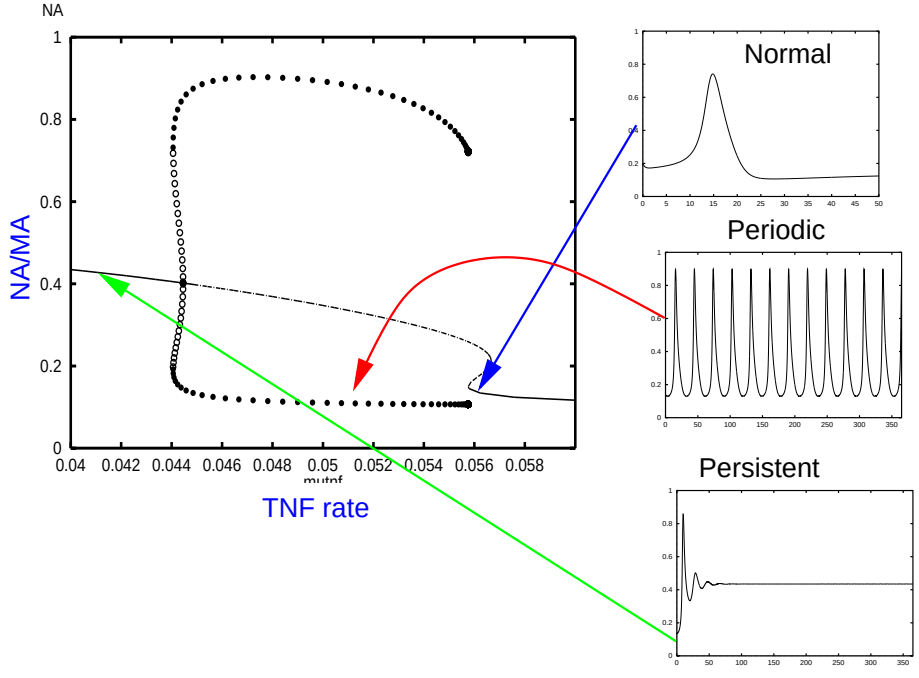






Towards a mechanistic view

As an example, consider TRAPS. This appears to caused by a mutation which slows the shedding of the TNF receptor. In the simple “excitable” model, changing the decay of the TNF receptor has a profound effect.

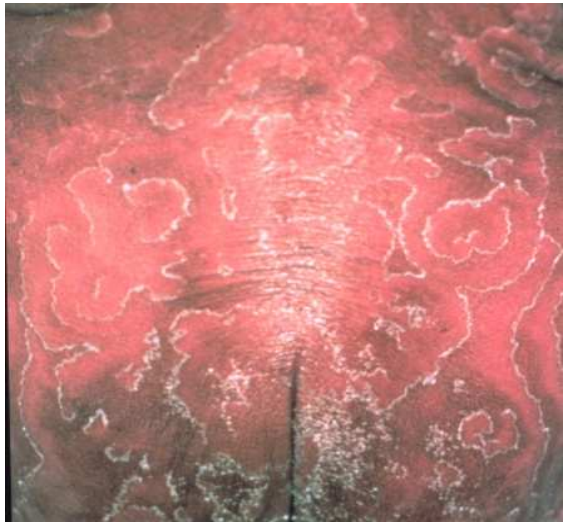


Rash theory revisited

- Lee Segel (1992) speculated that some rashes could result from “pattern formation” mechanisms
- $(V(x,t), I(x,t))$ virus and “immune” response are like **activator-inhibitor**
- Type I/II patterns stationary Turing like/moving
- No real equations or model
- Gilmore and Landman (2005) suggest Erythema gyratum repens due to excitable medium and simulate CA model and chemical reaction (!) model.

Some interesting rashes

Erythema gyratum repens

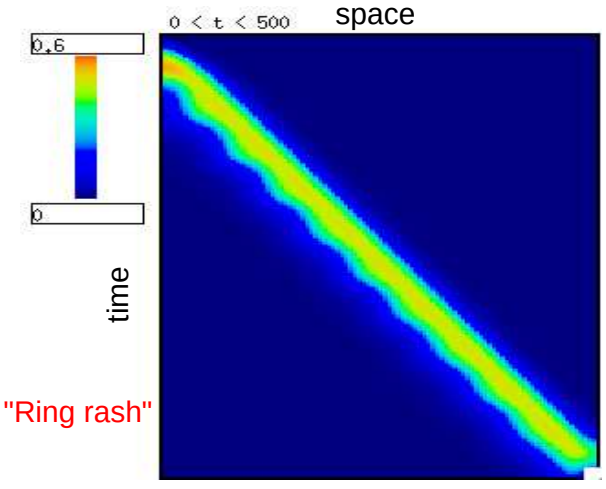


Geographic tongue

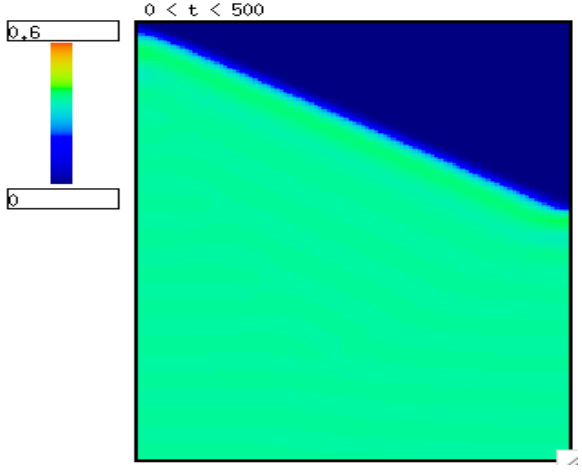
Erythema migrans (Lyme disease)

Space 1

MA/NA −− Pathogen model

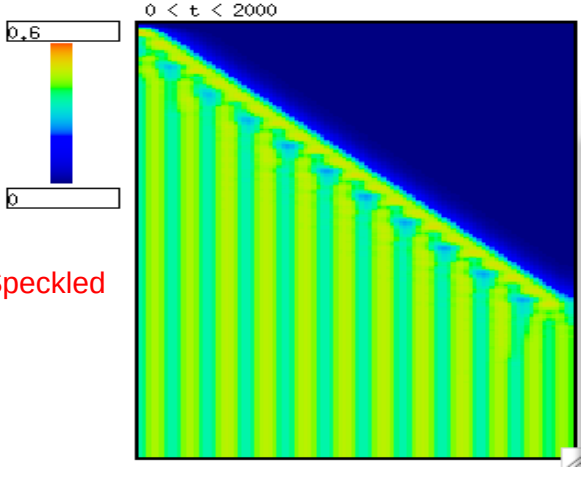


"Ring rash"

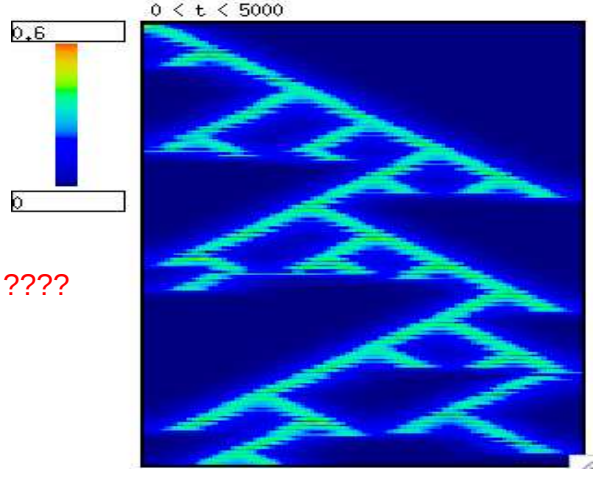


Solid

Rash

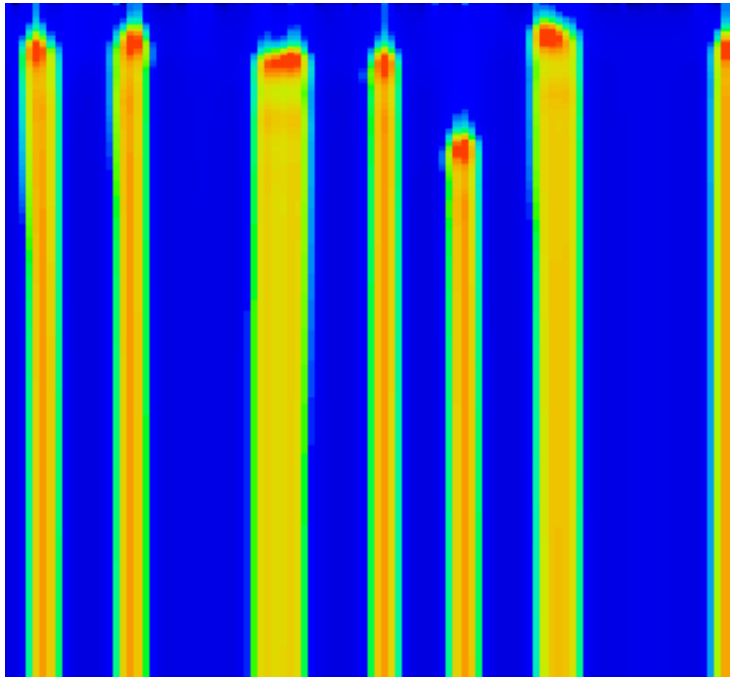


Speckled

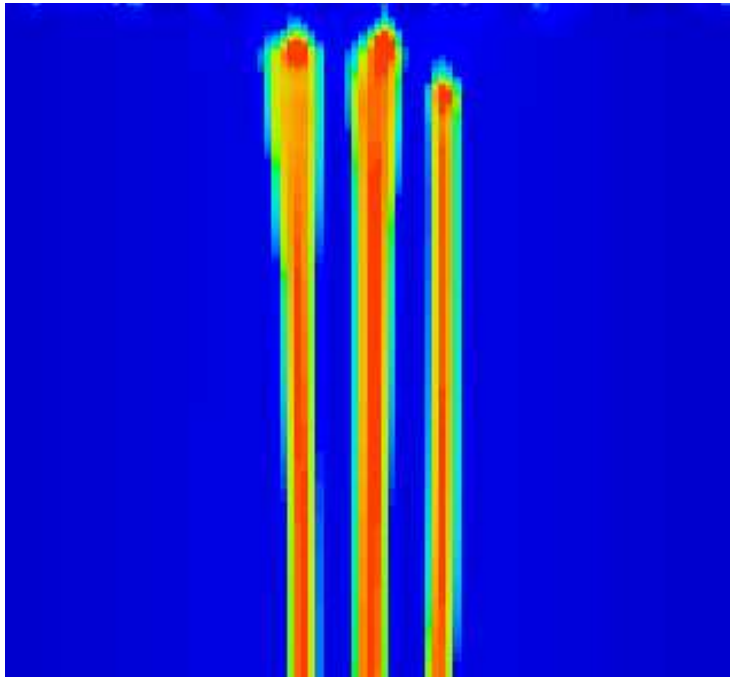


????

Space 2



Irregular rash



Lyme disease ring

Future

- Inflammation is a complex dynamic process than can benefit from the tools of nonlinear dynamics
- Starting with simple models, buiild increasingly comples ones and use parameter fitting tools
- More and more experimental data can be used to constrain the models
- Current work on influenza and the role of the inflammatory process, malaria (midgut of the mosquito), competition of bacteria in the gut during inflammation, MODS, etc