State Dependent Life History Theory and Stem Cell Biology

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Outline

- Why an evolutionary ecologist should care about stem cell biology (other than the coolness factor)
  - The Hematopoietic Stem Cell (HSC) system is a great one to think about.
  - State dependent life history theory for everyone -- the provigenic insect (and some experiments)
  - State dependent life history theory and the quiescence of HSCs
  - State dependent life history theory and the penultimate differentiation of HSC products: The Stem Cell Functional Response (SCFR) and Fitness Control Hypothesis (FCH)
Why Evolutionary Ecologists Should Care About Stem Cells: Organismal Performance is Intimately Connected to Stem Cells

Germ stem cells --->
Oocytes -->
Mature eggs --->
Reproductive Success
UV -->
Damage -->
Apoptosis -->
Cellular renewal
Diving -->
Hypoxia and ischemia -->
Reperfusion -->
Apoptosis --> Cellular Renewal

Schuler et al. 2010. PNAS
107:419-423
Sebastes aleutianus (rougheye rockfish), possibly born the same year as Darwin (maximum age of S. aleutianus ~205 yrs)

Shortraker rockfish (S. borealis) caught in March 2007; estimated 95-115 years old

...Negligible Senescence
A bit of stem cellology.

• Stem cells have the ability to both self-renew and to differentiate.

• Found as transient populations during development and growth of an organism and as stable populations in adult tissues.

• The niche of the stem cell is the local microenvironment that supports the maintenance, renewal, and differentiation of stem cells.
The Fundamental Division: Symmetric or Asymmetric Renewal

But Nothing Can Happen Without The Support of the Niche and the Organism


Stem Cell Dynamics in Response to Nutrient Availability

McLeod et al. 2010. Current Biology 20:1-6
The Hematopoietic Stem Cell (HSC) System is a demand-control system

Demonstration of the Demand Control (Cheshier et al 2007 Stem Cells and Development 16:707): Perturbation Experiment #1

- Bleed mice on days 3, 6, 9
- Sacrifice on day 10 and measure markers of HSC activity
And for Lymphoid Cells [Baldridge et al 2010 (Nature 465:793)]: Quiescent HSCs are activated in response to infection; Perturbation Experiment #2
The Beautiful and Classic Experiment of Till et al. 1964. PNAS 51:29

Fig. 2.—Schematic outline of the spleen-colony technique.
Lots of Epigenetic variation

Mean number of progeny cells (4.5) << Variance in the number of progeny cells (81.4)

==> over dispersion

Fig. 5.—Cumulative distribution of CFU per colony in individual 12-day spleen colonies (cf. Fig. 4). The smooth curve represents a gamma distribution having the same mean and variance as the experimental data.
A simple but useful heuristic

Poisson activity of cells:

$$\Pr\{\text{a cell does something in the next } dt \} = rdt + o(dt)$$

If the rate parameter has a gamma density with parameters $\nu$ and $\alpha$ then the resulting compound density has mean

$$m = \frac{\nu}{\alpha}$$

and variance

$$Var = m + \frac{m^2}{\nu}$$
Quick and dirty (method of moments) fit.

Two Questions:
Q1. Why are stem cells mainly quiescent?
Q2. Why is there so much variability?
These are More Than Academic Questions  12 Sept 2007: 50th Anniversary of BMTs

INTRAVENOUS INFUSION OF BONE MARROW IN PATIENTS RECEIVING RADIATION AND CHEMOTHERAPY*

E. Donnall Thomas, M.D.,† Harry L. Loghte, Jr., M.D.,‡ Wan Ching Lu, Ph.D.,§ and Joseph W. Ferrerele, M.D.¶

Timeline Showing Numbers of Bone Marrow Transplantations and Advances in the Field, 1957–2006.

BMT denotes bone marrow transplantation, and HLA human leukocyte antigen. Data are from the Center for International Blood and Marrow Transplant Research.

FA Appelbaum. 2007. NEJM 357:1472
Today, we know much about mechanism, but little about how natural selection has shaped these mechanisms.
Key features usually not treated in stem cell modeling

• Signals from remote sources (transit amplifying and fully differentiated cells)

• The niche has limited resources that can flow to stem cells
**Key features usually not treated in stem cell modeling**

- Signals from remote sources (transit amplifying and fully differentiated cells)
- The niche has limited resources that can flow to stem cells

*Till et al knew this in 1964*
Stochastic transitions of HSCs and their descendants

* = the usual suspects ("p+q+r=1")

Mangel & Bonsall 2008 PLoS ONE, 3, e1591
There is Both Positive and Negative Feedback
This is Fundamentally Stochastic System

\[
\begin{align*}
\Delta S &= S(t + \Delta t) - S(t) \\
\Delta A &= A(t + \Delta t) - A(t) \\
\Delta D &= D(t + \Delta t) - D(t)
\end{align*}
\]

Symmetric renewal

\[
\rho_1 = \Pr\{\Delta S = 1, \Delta A = 0, \Delta D = 0 \mid S(t) = s, A(t) = a, D(t) = d\}
= r_1 s \ln \left( \frac{K}{s} \right) \Delta t + o(\Delta t)
\]

Asymmetric renewal

\[
\rho_2 = \Pr\{\Delta S = 0, \Delta A = 1, \Delta D = 0 \mid S(t) = s, A(t) = a, D(t) = d\}
= r_2 s \ln \left( \frac{K}{s} \right) \Phi_2(a, d) \Delta t + o(\Delta t)
\]

Symmetric differentiation

\[
\rho_3 = \Pr\{\Delta S = -1, \Delta A = 2, \Delta D = 0 \mid S(t) = s, A(t) = a, D(t) = d\}
= r_3 s \ln \left( \frac{K}{s} \right) \Phi_3(a, d) \Delta t + o(\Delta t)
\]

Apoptosis or migration out of the niche

\[ \rho_4 = \Pr\{\Delta S = -1, \Delta A = 0, \Delta D = 0 \mid S(t) = s, A(t) = a, D(t) = d\} \]
\[ = \mu_4 s \Delta t + o(\Delta t) \]

Transit amplifying cell division

\[ \rho_5 = \Pr\{\Delta S = 0, \Delta A = 1, \Delta D = 0 \mid S(t) = s, A(t) = a, D(t) = d\} \]
\[ = r_5 a \Delta t + o(\Delta t) \]

Transit amplifying cells apoptosis

\[ \rho_6 = \Pr\{\Delta S = 0, \Delta A = -1, \Delta D = 0 \mid S(t) = s, A(t) = a, D(t) = d\} \]
\[ = (1 - \phi)\mu_6 a \Delta t + o(\Delta t); \phi < 1 \]
Transit amplifying cell commitment to differentiation

$$\rho_7 = \Pr\{\Delta S = 0, \Delta A = -1, \Delta D = 1 \mid S(t) = s, A(t) = a, D(t) = d\} = \phi \mu_6 a \Delta t + o(\Delta t)$$

Differentiated cell mortality

$$\rho_8 = \Pr\{\Delta S = 0, \Delta A = 0, \Delta D = -1 \mid S(t) = s, A(t) = a, D(t) = d\} = \mu_8 d \Delta t + o(\Delta t)$$

The phenotype of the stem cell clone

$$\{r_1, r_2, r_3, r_5, \Phi_2(a,d), \Phi_3(a,d), \mu_4, \mu_6, \mu_8, \phi\}$$
The Central Limit Theorem for Population Processes Leads to the “Corresponding” ODE system

\[
\frac{dS}{dt} = S \ln\left( \frac{K}{S} \right) \left[ r_1 - r_3 \Phi_3(A, D) \right] - \mu_4 S
\]

\[
\frac{dA}{dt} = S \ln\left( \frac{K}{S} \right) \left[ r_2 \Phi_2(A, D) + 2r_3 \Phi_3(A, D) \right] + r_5 A - \mu_6 A
\]

\[
\frac{dD}{dt} = \phi \mu_6 A - \mu_8 D
\]

Some typical outputs
The ODE captures the mean behavior remarkably well
State Dependent Life History Theory: The Pro-ovigenic Parasitoid
Aphytis -- Parasitoid of Scale Insects

Average size of a daughter from a clutch of size $c$

$$S(c) = 0.245 - 0.0223(c - 1)$$

Number of eggs as a function of size

$$E(S) = \max\{181.8S(c) - 26.7, 0\}$$

Expected number of grandoff-spring when a clutch of size $c$ is laid

$$f(c) = cE(S(c))$$
Thus, *Aphytis* has an optimal clutch size.
The Answer

State variable

$X(t) = \text{number of eggs at the start of period } t$
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\[ X(t) = \text{number of eggs at the start of period } t \]

Encounter

\[ \lambda = \Pr\{\text{encounter a host in a single period of search}\} \]
The Answer

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Dynamics determined by oviposition behavior

\[ X(t+h(c)) = X(t) - c \]
The Answer

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Accumulated fitness

\[ F(x,t) = \text{maximum expected accumulated number of potential grandchildren from } t \text{ to } T \text{ [time of death] given that } X(t)=x \]
**The Answer**

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**Survival**

\[ e^{-m} \text{ during search} \quad e^{-mh(c)} \text{ during oviposition} \]
Evaluating Fitness and the Method of Stochastic Dynamic Programming

\[ F(x,t) = \text{maximum expected accumulated number of potential grandchildren from } t \text{ to } T \text{ given that } X(t) = x \]

\[
F(x,t) = (1 - \lambda)e^{-m}F(x,t+1) + \lambda \max_c \{ f(c) + e^{-mh(c)}F(x-c,t+h(c)) \}
\]

Since no fitness is accumulated after \( T \)

\[ F(x,T) = 0 \]

An equation of stochastic dynamic programming, solved by the method of backward induction
Into the lab

We can vary encounter rate

\[ F(x,t) = (1 - \lambda) e^{-m} F(x, t + 1) + \lambda \max_c \{ f(c) + e^{-mh(c)} F(x - c, t + h(c)) \} \]
Into the lab

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$$F(x,t) = (1 - \lambda)e^{-m}F(x,t + 1) + \lambda \max_c \left\{ f(c) + e^{-mh(c)}F(x - c,t + h(c)) \right\}$$

We can explore clutch size in relation to state

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\[ F(x,t) = (1 - \lambda)e^{-m} F(x,t + 1) + \lambda \max_c \{ f(c) + e^{-mh(c)} F(x - c, t + h(c)) \} \]

And the effects of mortality

\[ F(x,t) = (1 - \lambda)e^{-m} F(x,t + 1) + \lambda \max_c \{ f(c) + e^{-mh(c)} F(x - c, t + h(c)) \} \]
Predictions: How Clutch Depends Upon State and Mortality

![Graph showing clutch predictions](image-url)
Predictions: How Clutch Depends Upon State and Mortality

Quiz: What general pattern do we predict for later clutches?
Result of Rosenheim and Rosen (1991)

Fraction of clutches

Egg complement

- Clutch=1
- Clutch=2
- Clutch=3
Testing the Effects of Mortality with Leptopilina

- Only one egg at a time but two kinds of hosts: previously unparasitized (fitness increment $f_u$) or previously parasitized (fitness increment $f_p$)

$$f_u > f_p$$

$$F(x,t) = (1 - \lambda_u - \lambda_p)e^{-m}F(x,t+1) + \lambda_u \{f_u + e^{-m_{ov}}F(x-1,t+\tau)\}$$

$$+\lambda_p \max\{e^{-m}F(x,t+1), f_p + e^{-m_{ov}}F(x-1,t+\tau)\}$$
The Likelihood of Superparasitism Depends Upon Time and State
The Prediction of Superparasitism Depends Upon Mortality

Time to start superparasitism

Mortality during search
The Prediction of Superparasitism

Time to start superparasitism

Photoperiod manipulation

Mortality during search

Protocol

• Summer or late fall photoperiod/steady or dropping barometric pressure

• Previous experience with patches with unparasitized hosts or previously parasitize hosts
Protocol

• Summer or late fall photoperiod/steady or dropping barometric pressure

• Previous experience with patches with unparasitized hosts or previously parasitize hosts
The Prediction of Superparasitism

Time to start superparasitism

Mortality during seach

Mortality cue manipulation
A Result So Strong that One Didn’t Even Need Statistics

![Graph showing superparasitism levels under steady and dropping barometric pressure. The dropping pressure has a significantly higher superparasitism level, indicated by a taller bar.](image-url)
Some Other Applications of the State Dependent Theory of Offspring Number

- Evolution of marking pheromones
- Seasonal effects on superparasitism
- Information as a state variable
- Synovigenic parasitoids and plant feeding/host seeking or host feeding
- Testing in the field
Intermediate Conclusion: Phenotypic optimization models are topographic maps for natural selection and are testable.

How would an application to quiescence of HSCs look?
Condition the phenotype (Mangel & Bonsall 2008 PLoS ONE, 3, e1591)

\{K, r_1, r_2, r_3, r_5, \Phi_2(a,d), \Phi_3(a,d), \mu_4, \mu_6, \mu_8, \phi\}

Then characterize

• Flow of resources flow to the focal stem cell

• Threshold level of resources \( y_d \) for division

• Probability of error-free daughter cell, given current resources

• Performance of the organism depending upon the number of fully differentiated cells and accumulated at rate \( R_f(d) \)
**Fitness**

\[ F(y,s,a,d) = \text{maximum expected performance through the fully differentiated cells given that the focal stem cell has currently accumulated } y \text{ resources and that there are } s \text{ stem cells in the niche, } a \text{ transit amplifying cells in the body, and } d \text{ fully differentiated cells sending signals back to the niche} \]

- Determined from the fitness value of doing nothing, asymmetric division, symmetric division
- The SDP equation is a bit tricky, but solvable.
• At the end we have

\[ i^*(y,s,a,d) \]

the optimal decision for the focal stem cell, determined by its state, the phenotype of the niche, the number of stem cells in the niche, and the number of transit amplifying and fully differentiated cells in the body.

• Then forward Monte Carlo iteration to see properties of populations of cells.
The main result

About 1100 transitions

• 6.25% of them symmetric renewal

• 93.75% of them asymmetric renewal

• Average value of resources at the time of transition is 7.1, while minimum level is 5.5. Variance in resources is 0.7

• Average value of A+D at transitions is 10.8, variance is 53.5
The main result is encouraging…suggesting that there is much that can be learned from these approaches.
The Penultimate Differentiation of HSC Descendants: The Question

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How is the penultimate route determined?

Penultimate Differentiation of HSCs Products: The Experimental System

Dynamics of different stem cells (and doses) following engraftment traced in replicate mice

β-actin GFP donor

Wildtype host

Peripheral blood

FACS sorting of stem and progenitor cells

Transplant of cell doses into sublethally irradiated mice

Lineage re-population kinetics

\textsuperscript{a}Forsberg et al. 2006 Cell 126, 415-426
The Model

Donor Progenitor Cells

Long term (LT) Stem Cells
Short Term (ST) Stem Cells
Undifferentiated Progenitor Cells (UP)

Repopulating Lymphoid Cells
Repopulating Myeloid Cells

Original Lymphoid Cells
Original Myeloid Cells

\( r_p \)
\( r_d \rho \)
\( r_d(1-\rho) \)
\( r_l \)
\( r_m \)
\( \mu_{lh} \)
\( \mu_{mh} \)
The Stem Cell Functional Response (SCFR)

\[ \rho(l,m) = \text{Pr}\{\text{terminally differentiating cell goes the lymphoid rather than myeloid, given that there are currently } l \text{ lymphoid and } m \text{ myeloid cells in the body} \} \]

\[ \rho(l,m) = \frac{\alpha \left( \frac{m}{l} \right)^{\gamma}}{1 + \alpha \left( \frac{m}{l} \right)^{\gamma}} \]

In homeostasis, assume

\[ m : l \sim \kappa_m : \kappa_l \]

\[ \rho(\kappa_l,\kappa_m) = \rho_h \sim \frac{\kappa_l}{\kappa_l + \kappa_m} \]
\[
\rho_h = \frac{\alpha \left( \frac{\kappa_m}{\kappa_l} \right)^\gamma}{1 + \alpha \left( \frac{\kappa_m}{\kappa_l} \right)^\gamma}
\]

From which we determine

\[
\alpha = \left( \frac{\rho_h}{1 - \rho_h} \right) \left( \frac{\kappa_m}{\kappa_l} \right)^{-\gamma}
\]

Conclusion: there is a family of parameter values consistent with homeostasis
Every value along this line is consistent with homeostasis
But they will provide very different responses for the organism.
The Differential Equations Become More Complicated

\[ \frac{dS}{dt} = S \cdot \log(K / S)(r_s - r_p, \Phi_p(L_T, M_T))\Phi_s(L_T, M_T) - \mu_s S \]

\[ \frac{dP}{dt} = S \cdot \log(K / S)(r_p + 2r_p, \Phi_p(L_T, M_T))\Phi_s(L_T, M_T) + (\lambda - r_d)\Phi_p(L_T, M_T)P - \mu_p P \]

\[ \frac{dL}{dt} = r_d\Phi_p(L_T, M_T)P \rho(L_T, M_T) + (r_l - \mu_l)L \]

\[ \frac{dM}{dt} = r_d\Phi_p(L_T, M_T)P[1 - \rho(L_T, M_T)] + (r_m - \mu_m)M \]

\[ \frac{dL_h}{dt} = -\mu_lL \]

\[ \frac{dM_h}{dt} = -\mu_mM \]

**Observables**

\[ f_L(t) = \frac{L(t)}{L(t) + L_h(t)} \quad \quad f_M(t) = \frac{M(t)}{M(t) + M_h(t)} \]
Host Cells Just Die in a Transplant Experiment
And Transplanted Cells Grow

Not observable
And Transplanted Cells Grow

Not observable

Observable
With a Dynamic Pattern of Feedback Control
Could We Infer the SCFR from a Transplant Experiment?

Not from myeloid but maybe from lymphoid cells
Could We Infer the SCFR from a Transplant Experiment?

Not from myeloid but maybe from lymphoid cells
How About from a Lymphoid Perturbation Experiment?
How About from a Myeloid Perturbation Experiment?
Next steps:

To determine if model selection techniques will allow us to infer the SCFR from lymphoid and myeloid dynamics in transplant and perturbation experiments....
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To determine if model selection techniques will allow us to infer the SCFR from lymphoid and myeloid dynamics in transplant and perturbation experiments.

...and to find the right data

Intestinal Stem Cell Replacement Follows a Pattern of Neutral Drift

Carlos Lopez-Garcia, Allon M. Klein, Benjamin D. Simons, Douglas J. Winton

Science. 2010. 330:822
The Fitness Control Hypothesis (FCH) And Natural Selection for the SCFR

Let $F(l,m)$ be a measure of Darwinian fitness when density of lymphoid cells is $l$ and of myeloid cells is $m$. 
The Fitness Control Hypothesis (FCH) And Natural Selection for the SCFR

• Let \( F(l,m) \) be a measure of Darwinian fitness when density of lymphoid cells is \( l \) and of myeloid cells is \( m \).

• The *Fitness Control Hypothesis* is that

\[
\rho(l,m) = \frac{\partial F / \partial l}{\partial F / \partial m + \partial F / \partial m}
\]
The Fitness Control Hypothesis (FCH) And Natural Selection for the SCFR

Let $F(l,m)$ be a measure of Darwinian fitness when density of lymphoid cells is $l$ and of myeloid cells is $m$.

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Challenge: How to find $F(l,m)$?
The Fitness Control Hypothesis (FCH) And Natural Selection for the SCFR

• Let $F(l,m)$ be a measure of Darwinian fitness when density of lymphoid cells is $l$ and of myeloid cells is $m$.

• The *Fitness Control Hypothesis* is that

$$\rho(l,m) = \frac{\partial F / \partial l}{\partial F / \partial m + \partial F / \partial m}$$

• Challenge: How to find $F(l,m)$?

• Answer: state dependent life history theory as implemented by stochastic dynamic programming
A Simple Version with the Focus on a Mature Individual with Plentiful Food

In a unit of time may encounter predator or disease organism; the probabilities are

$$\beta_p, \beta_d$$
A Simple Version with the Focus on a Mature Individual with Plentiful Food

In a unit of time may encounter predator or disease organism; the probabilities are

\[ \beta_p, \beta_d \]

Given \( m \) myeloid cells, the probability of escaping the predator is

\[ \lambda_p(m) \]
A Simple Version with the Focus on a Mature Individual with Plentiful Food

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Given $l$ lymphoid cells, the probability of overcoming the disease is

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A Simple Version with the Focus on a Mature Individual with Plentiful Food

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Given \( l \) lymphoid cells, the probability of overcoming the disease is

\[ \lambda_d(l) \]

In each period, lifetime reproductive success is fitness incremented by

\[ \delta f \]
Also in a unit of time

The ‘usual’ loss of lymphoid and myeloid cells is

\[ l_0, m_0 \]
Also in a unit of time

The ‘usual’ loss of lymphoid and myeloid cells is

$$l_0, m_0$$

If a disease organism is encountered and overcome, then the additional loss of lymphoid cells is

$$l_d$$
Also in a unit of time

The ‘usual’ loss of lymphoid and myeloid cells is

\[ l_0, m_0 \]

If a disease organism is encountered and overcome, then the additional loss of lymphoid cells is

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If a predator is encountered and successfully evaded, then the additional loss of myeloid cells is

\[ m_d \]
Also in a unit of time

The ‘usual’ loss of lymphoid and myeloid cells is

\[ l_0, m_0 \]

If a disease organism is encountered and overcome, then the additional loss of lymphoid cells is

\[ l_d \]

If a predator is encountered and successfully evaded, then the additional loss of myeloid cells is

\[ m_d \]

A total of \( P \) HSC descendants differentiate so that the constraint on new lymphoid and myeloid cells is

\[ l' + m' = P \]
Then

\[ F(l,m) = \delta f + \max_{m' + l' = P} e^{-\mu_c} [(1 - \beta_p)(1 - \beta_d)F(l - l_0 + l', m - m_0 + m') + \beta_p (1 - \beta_d)\lambda_p(m)F(l - l_0 + l', m - m_p + m') + \beta_d (1 - \beta_p)\lambda_d(l)F(l - l_d + l', m - m_o + m') + \beta_d \beta_p \lambda_p(m)\lambda_d(l)F(l - l_d + l', m - m_p + m')] \]

And we estimate

\[ \rho(l,m) = \frac{F(l + 1,m) - F(l,m)}{F(l + 1,m) - F(l,m) + F(l,m + 1) - F(l,m)} \]
\( \rho(l,m) \) for \( \beta_p = 0.05, \beta_d = 0.002, P = 5 \) cells per period
\( \rho(l,m) \) for \( \beta_p = 0.035, \beta_d = 0.008, P = 5 \) cells per period
\( \rho(l,m) \) for \( \beta_p = 0.045, \beta_d = 0.001, P = 10 \) cells per period
Next steps:

To couple computation of the SCFR from the Fitness Control Hypothesis to the HSC dynamics for transplant and perturbation experiments...and to find the right data.
Conclusions

• Ultimate ("why") questions and proximate ("how") questions can and should interact with each other and state dependent life history theory is the natural way to do this.

• Stem (and associated descendent) cell dynamics are indeed variable and complex, but much of that variability can be understood.

• Deterministic models can reveal evolutionary process through the analysis of both transplantation and perturbation experiments

• Discriminating between different mechanistic (evolutionary) processes is feasible using a model choice framework
• We can link the parameters in the SCFR

\[ \rho(l,m) = \frac{\alpha \left( \frac{m}{l} \right)^\gamma}{1 + \alpha \left( \frac{m}{l} \right)^\gamma} \]

to the evolutionary ecology of the organism through the FCH by estimating \( \alpha \) and \( \gamma \) using those heat maps.

• The environment, through the risks of predation and disease, will shape the SCFR through the FCH

• There is tremendous scope for developing strong links across different levels of biological organization through stem cell biology
Is this just too much speculation?

The selection of ideas

• Genes

• The double helix

• Channels in membranes

• Reaction and diffusion as mechanisms of development

• The threshold level of susceptibles

• Mosquitos transmit malaria

• Molecular motors as thermal ratchets
Well, is it practical?

Calf Injury Leading to DVT
Patient MM, age 59
Well, is it practical?

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Well, is it practical?

Heparin
- Discovered 1916
- Clinical trials 1935
- Natural function still unclear

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Coumadin (WARFarin)
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- 4 months for next 1.8 g
- Rodent poisons 1941-51
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The benefits of science are neither apparent nor immediate for individuals -- Kevin Kelley, 2010

Calf Injury Leading to DVT
Patient MM, age 59
There is much to be done and not a moment to be lost