GENERAL BRANCHING PROCESSES: THEORY AND BIOLOGICAL APPLICATIONS

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POPULATION DYNAMICS

Goal: to describe and analyze properties of populations of reproducing individuals.

1. Deterministic methods (e.g., differential equations)

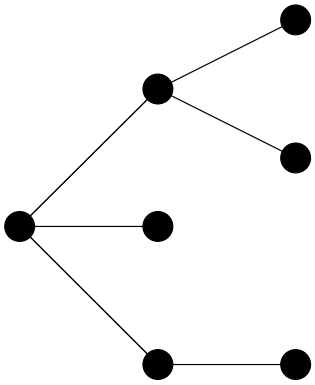
- "top down," start on population level, $\frac{dx}{dt} = f(x(t))$
- no connection between individuals and population
- only describe expected values, no extinction
- easy to deal with dependencies, feedback, "nonlinearity"

2. Stochastic methods (e.g., branching processes)

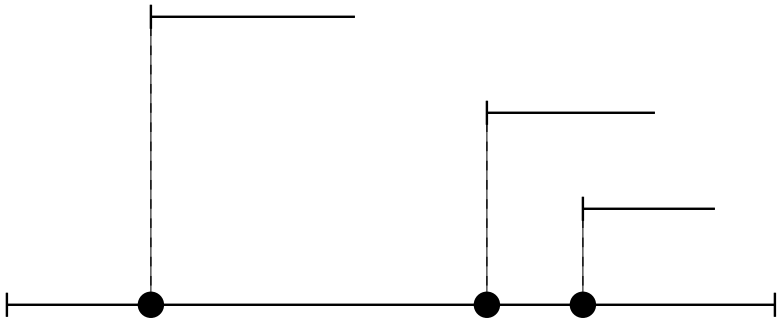
- "bottom up," start on individual level, $P(k \text{ children}) = p_k$
- relate individual behavior to population behavior
- expected values, variances, large deviations, extinction
- difficult to deal with dependencies, feedback, "nonlinearity"

BRANCHING PROCESSES

1. Galton-Watson process, discrete time, synchronized generations



2. General branching process, continuous time, overlapping generations



GALTON-WATSON PROCESS

- Number of children X, random variable on $\{0, 1, 2, ...\}$

- Size of nth generation:

$$Z_n = \sum_{k=1}^{Z_{n-1}} X_k, \ n = 1, 2, ... \quad (Z_0 \equiv 1)$$

- Growth rate: m^n, where $m = E[X]$

- Convergence: $\dfrac{Z_n}{m^n} \to W$ as $n \to \infty$.

GENERAL (CRUMP-MODE-JAGERS) BRANCHING PROCESS

• Reproduction process, ξ: point process on $[0, \infty)$

$$\xi(a) = \int_0^a \xi(dt) = \text{number of children up to age } a$$

• Mean reproduction process $\mu(a) = E[\xi(a)]$, $\mu(dt) = E[\xi(dt)]$

• Growth rate: $e^{\alpha t}$, where *Malthusian parameter* α solves the equation

$$\widehat{\mu}(\alpha) = \int_0^\infty e^{-\alpha t} \mu(dt) = 1$$

• Galton-Watson process: $\xi(dt) = X\delta_1(dt)$,

$$\xi(a) = \begin{cases} 0 & \text{if } a < 1 \\ X & \text{if } a \geq 1 \end{cases}$$

In this case,

$$\int_0^\infty e^{-\alpha t} \mu(dt) = me^{-\alpha} = 1$$

gives $\alpha = \log m$ and $e^{\alpha t} = m^n$.

RANDOM CHARACTERISTICS

• random characteristic χ, stochastic process, $\chi(a)$: contribution of an individual at age a

• χ-counted population

$$Z_t^\chi = \sum_{x \in I} \chi_x(t - \tau_x)$$

where

I =set of all individuals
τ_x=birth time of individual x, age $t - \tau_x$ at time t

Examples:

1. $\chi(a) = I_{R_+}(a)$ – indicator of being born, Z_t^χ = number of individuals born before t

2. $\chi(a) = I_{[0,L)}(a)$ – indicator of being alive, Z_t^χ = number of individuals alive at time t

CONVERGENCE RESULT

As $t \to \infty$,

$$e^{-\alpha t} Z_t^{\chi} \to c\, W$$

where W is a random variable and

$$c = \int_0^{\infty} e^{-\alpha t} E[\chi(dt)]$$

In the limit, χ enters only as a constant. Thus:

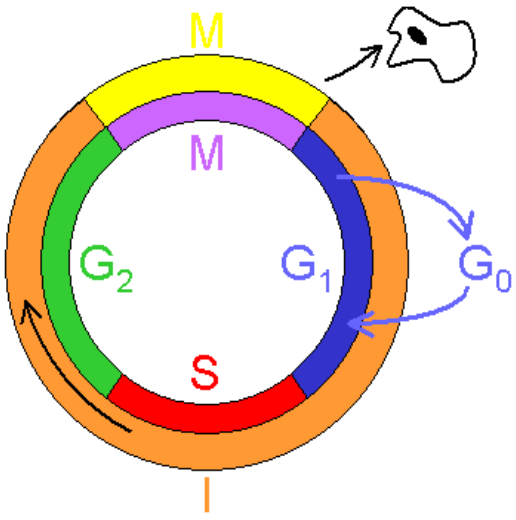
$$\frac{Z_t^{\chi_1}}{Z_t^{\chi_2}} \to \frac{c_1}{c_2}$$

Asymptotic stability, for example stable age distribution.

CELL POPULATIONS WITH QUIESCENCE

(O., *Journal of Biological Dynamics*, **2(4)**, 2008)

Cell cycle:



(www.knowledgerush.com)

G_1 phase – growth and preparation for DNA synthesis

S (synthesis) phase – DNA replication

G_2 phase – growth and preparation for division

M(mitosis) phase – cell division

G_0 phase – quiescence, possible at restriction point

PDE MODEL

Arino, Sànchez, Webb (1997)
Dyson, Villella-Bressan, Webb (2002)

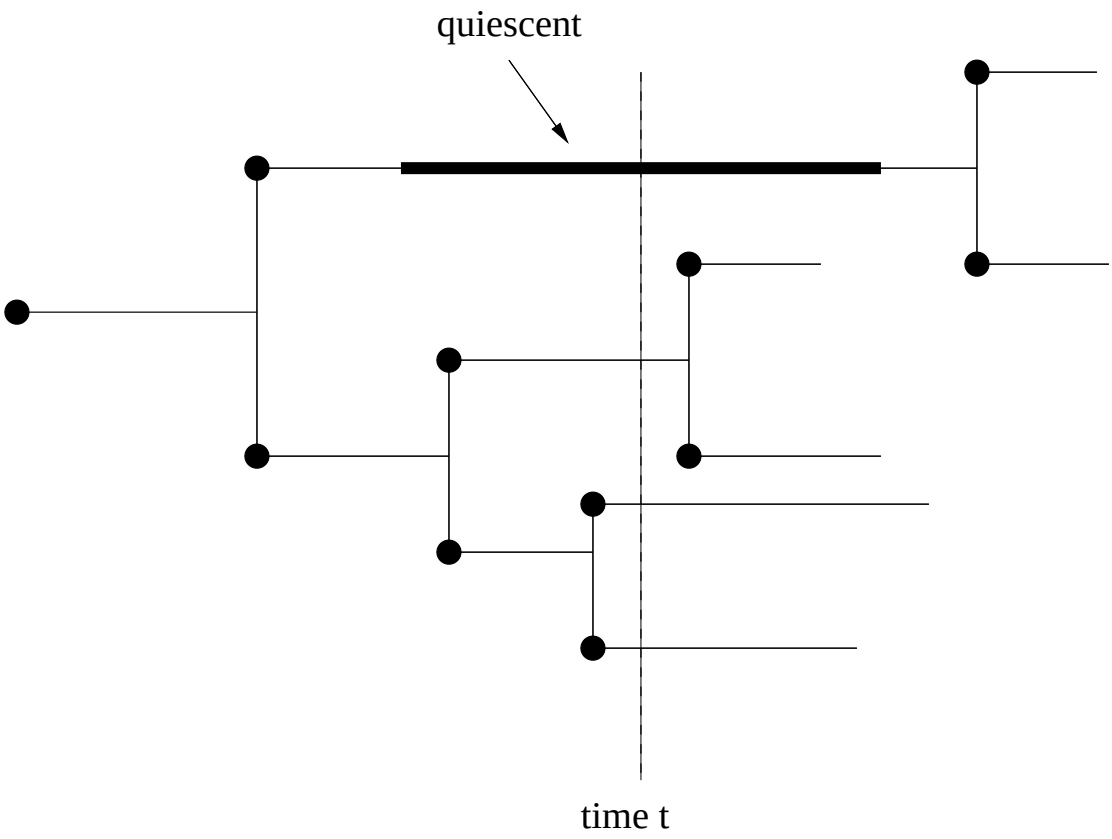
$p(a,t)$: density of proliferating cells
$q(a,t)$: density of quiescent cells

$$\begin{cases} \dfrac{dp}{dt} + \dfrac{dp}{da} = -(\mu(a) + \sigma(a))p(a,t) + \tau(a)q(a,t) \\ \dfrac{dq}{dt} + \dfrac{dq}{da} = -\sigma(a)p(a,t) - \tau(a)q(a,t) \end{cases}$$

μ: division rate
σ, τ: transition rates

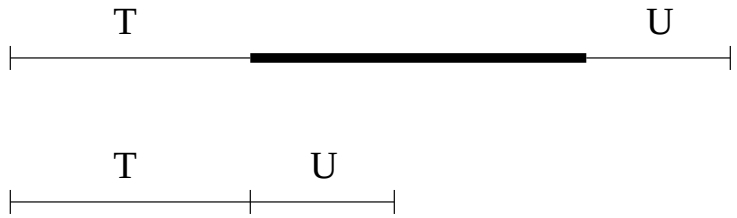
Lots of conditions $\Rightarrow$ asynchronous exponential growth, convergence toward stable proportion of quiescent cells

BRANCHING PROCESS MODEL



Fraction 1/4 of quiescent cells at time t. As $t \to \infty$?

LIFETIMES AND GROWTH RATE



$$L = \begin{cases} T + U & \text{with prob } 1 - q \\ T + G_0 + U & \text{with prob } q \end{cases}$$

Binary splitting, no death: $\xi(dt) = 2\delta_L(dt),\ \mu(dt) = 2F_L(dt)$.

Malthusian parameter given by

$$2\widehat{F}_L(\alpha) = 2(1-q)\widehat{F}_{T+U}(\alpha) + 2q\widehat{F}_{T+G_0+U}(\alpha) = 1$$

Laplace transform: $\widehat{F}(\alpha) = \int_0^\infty e^{-\alpha t} F(dt)$

CHARACTERISTICS AND ASYMPTOTICS

Quiescent cells:

$$\chi_q(a) = I\{Q \cap \{T < a, T + G_0 > a\}\} = \begin{cases} 1 & \text{if quiescent at age } a \\ 0 & \text{otherwise} \end{cases}$$

All cells:

$$\chi(a) = I\{L > a\} = \begin{cases} 1 & \text{if alive at age } a \\ 0 & \text{otherwise} \end{cases}$$

Fraction of quiescent cells:

$$Q(t) = \frac{Z_t^{\chi_q}}{Z_t^{\chi}} \to \frac{c_q}{c}$$

where

$$c_q = q \int_0^\infty e^{-\alpha t} P(T < t < T + G_0) dt$$

$$c = \int_0^\infty e^{-\alpha t} P(L > t) dt$$

AN EXAMPLE

T, U, G_0 independent $\Gamma(3,1)$

Malthusian parameter:

$$\frac{2(1-q)}{(1+\alpha)^6} + \frac{2q}{(1+\alpha)^9} = 1$$

$q = 0.9$ gives $\alpha \approx 0.08$ and $c_q/c \approx 0.30$ so

$$Q(t) \to 0.30 \quad \text{as } t \to \infty$$

How does $Q(t)$ approach its limit?

RENEWAL THEORY

For any general branching process:

$$E[Z_t^\chi] = E[\chi(t)] + \int_0^t E[Z_{t-u}^\chi]\mu(du)$$

with solution

$$E[Z_t^\chi] = \sum_{n=0}^{\infty} \int_0^t E[\chi(t-u)]\mu^{*n}(du)$$

$\mu^{*n}(t)$ = expected number of individuals from the nth generation born before time t.

Here:

$$\mu^{*n}(du) = 2^n F^{*n}(du)$$

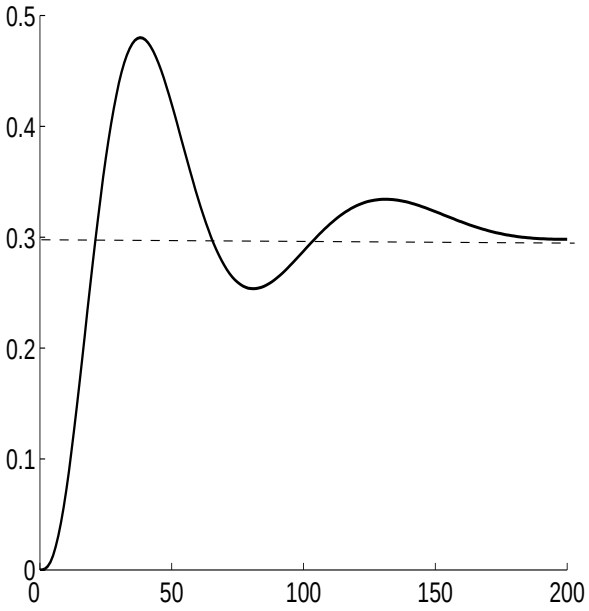
where

$$F^{*n}(du) = \sum_{k=0}^{n} \binom{n}{k} q^k (1-q)^{n-k} F_T^{*n} * F_U^{*n} * F_{G_0}^{*k}(du)$$

BACK TO EXAMPLE

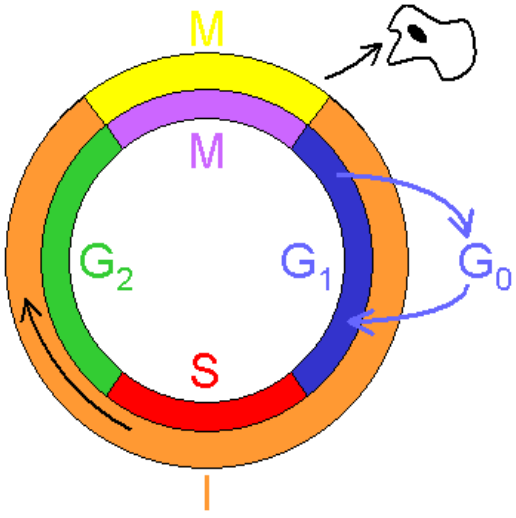
Approximation:

$$E[Q(t)] \approx \frac{E[Z_t^{\chi_q}]}{E[Z_t^{\chi}]} \to 0.30$$



CELL CYCLE DESYNCHRONIZATION

Cell cycle:



(www.knowledgerush.com)

Consider $Q(t)$: fraction of cells in S phase. Asymptotics, period, rate of convergence of $Q(t)$.

Joint with Thomas "Ollie" MacDonald, math major, Trinity University.

THE MODEL

- random lifetime $L = G_1 + S + G_2 + M$, cdf F
- reproduction by splitting, $\xi(dt) = 2\delta_L(dt), \mu(dt) = 2F(dt)$
- Malthusian parameter: $2\int_0^\infty e^{-\alpha t} F(dt) = 1$

Random characteristic counting cells in S phase:

$$\chi_S(a) = I\{G_1 \leq a \leq G_1 + S\}$$

Random characteristic counting cells alive:

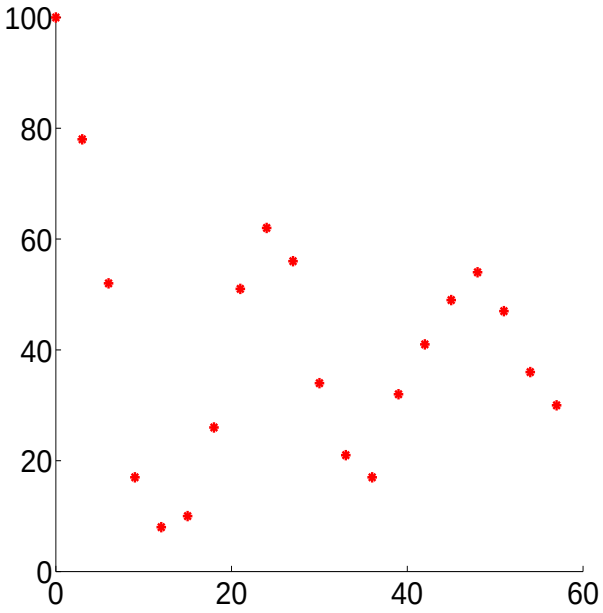
$$\chi(a) = I\{L > a\}$$

As $t \to \infty$, $Q(t) \to \dfrac{c_q}{c}$.

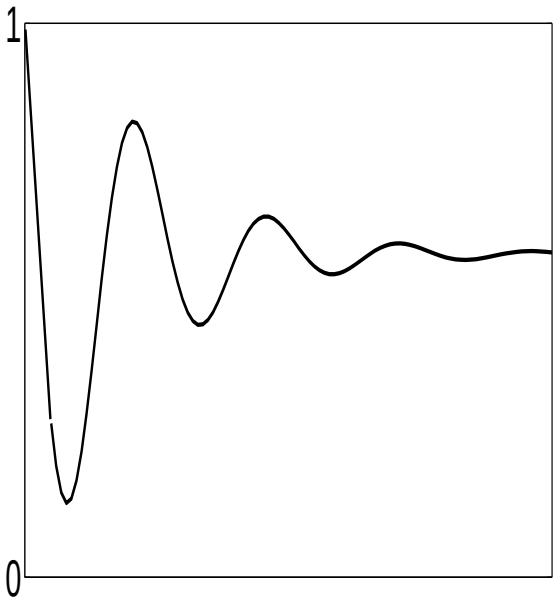
EXPERIMENTAL DATA

(Chiorino, Metz, Tomasoni, Ubezio, *J Theor Biol*, **208**, 2001)

Cells forced to start in S phase (synchronization). Percentage of cells in S phase as a function of time:



Our $Q(t)$:



Whence the initial linear part?

For small t, the ancestor dominates:

$$E[Z_t^\chi] = E[\chi(t)] + \int_0^t E[Z_{t-u}^\chi]\mu(du) \approx E[\chi(t)]$$

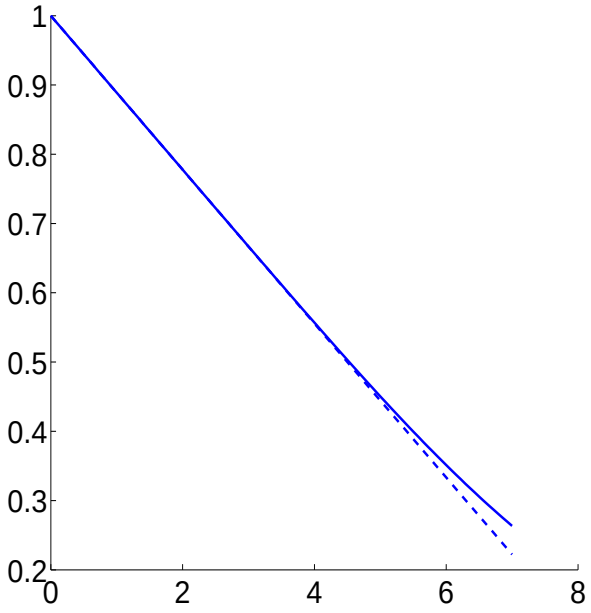
Counting cells in S phase:

$$\chi_S(a) = I\{G_1 \le a \le G_1 + S\}$$

Forced start in S phase: observe at time $G_1 + US + t$. Ancestor's contribution:

$$E[\chi_S(t)] = P(G_1 \le t + G_1 + US \le G_1 + S)$$

$$= P(S(1-U) \ge t) \approx 1 - \frac{t}{E[S]}$$



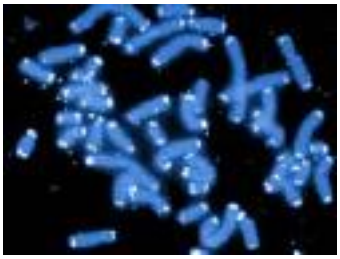
LOSS OF TELOMERES

Collaboration with Dr. Alison Bertuch, Baylor College of Medicine.

• Telomere: end of chromosome, shorten during replication.

• Length reaches critical point, cell division stops – senescence, Hayflick limit.

• Aging, cancer, forensics.

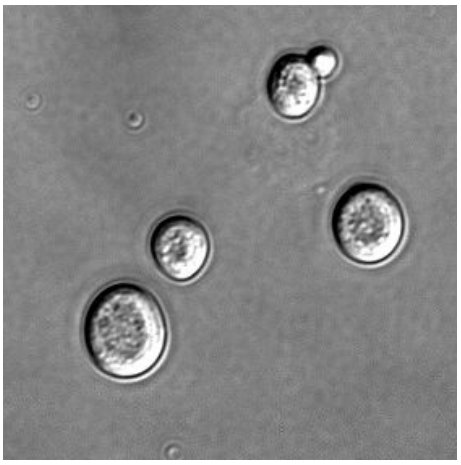
 (www.scinexx.de)

• Previous branching process models:

Arino, Kimmel, and Webb, *J. Theor. Biol.* **177** (1995)

O. and Kimmel, *Math. Biosci.* **1** (1999)

• Saccharomyces cerevisiae: important model organism (and SNPA).

 (Wikipedia)

• A mother cell produces many daughter cells – general branching process.

• Telomeres shorten in both mother and daughter.

• At critical length, no further division.

• Individual cells also age – finite number of offspring independently of telomere length (replicative lifespan).

BRANCHING PROCESS MODEL

• Need **multi-type** branching process: type is telomere length.

• A mother can have N daughters, $P(N = k), k = 0, 1, 2, ..$

(O. and Kimmel: $N \equiv \infty$, polynomial population growth)

• Times between budding events $L_1, L_2, ...$ i.i.d. with cdf F.

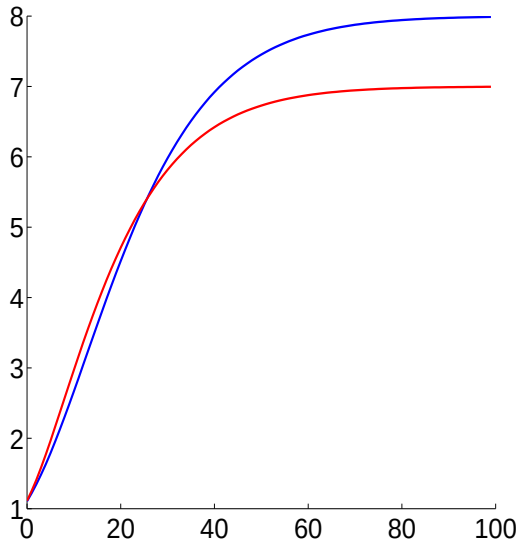
• $p_{i,j}(k)$: probability that kth daughter has telomere length j if mother initially has telomere length i.

• Let 0 be critical length: $p_{0,j}(k) \equiv 0$

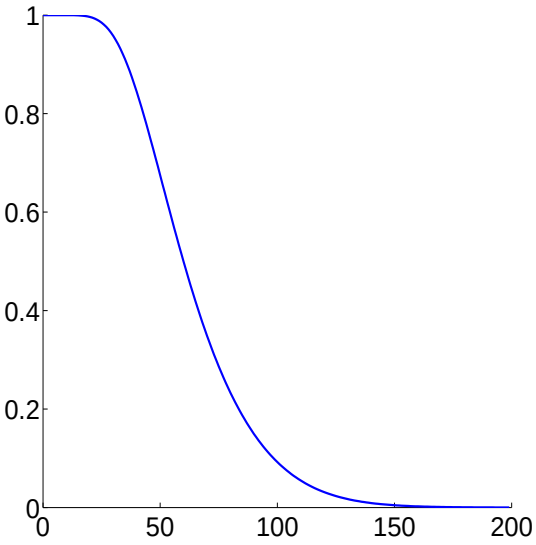
• Number of cells at time t:

$$E_i[Z_t^\chi] = \sum_{j=0}^{i} \sum_{n=0}^{\infty} \sum_{k_1,...k_n=1}^{\infty} \prod_{l=1}^{n} p_{ij}(k_l)^{*n} P(N \geq k_l) F^{*(k_1+...+k_n)}(t)$$

POPULATION GROWTH



FRACTION OF PROLIFERATING CELLS



COLLABORATORS

Ollie MacDonald, math major, Trinity University

Dr. Alison Bertuch, Baylor College of Medicine