Language Design and Implementation for Computational Modeling, Simulation and Visualization

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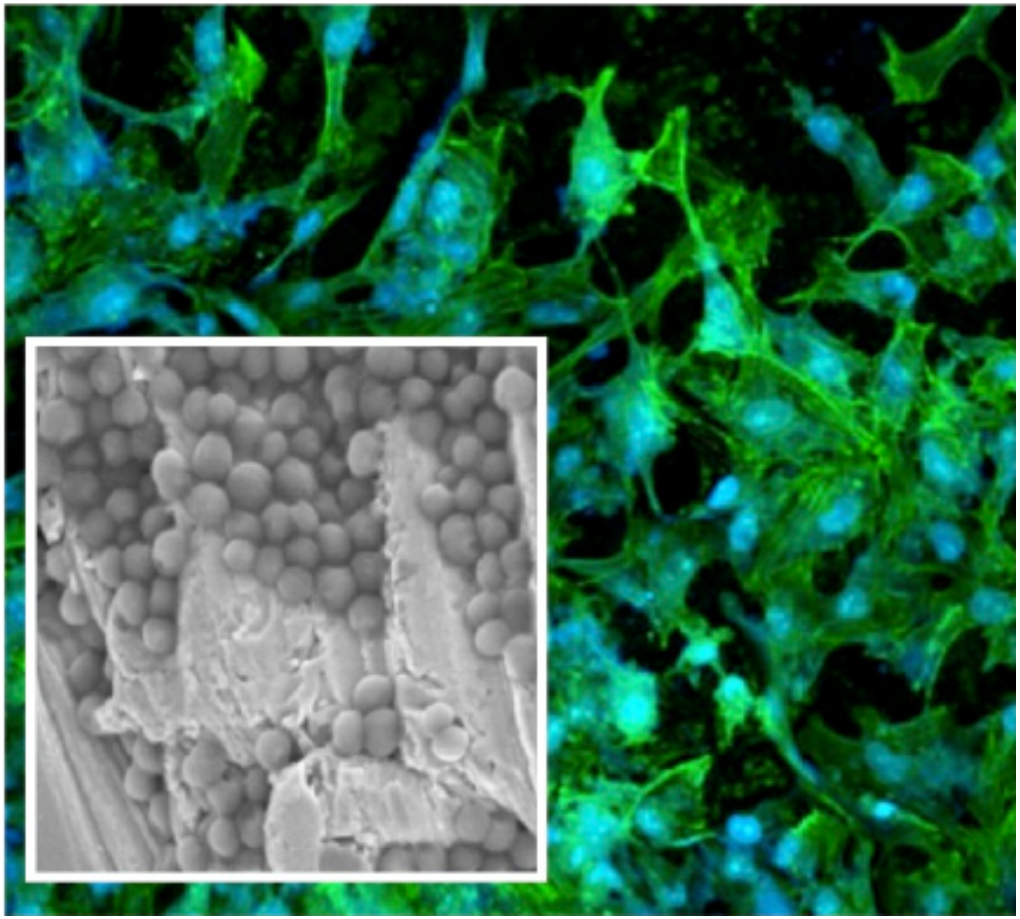
Stevens Institute of Technology, NJ

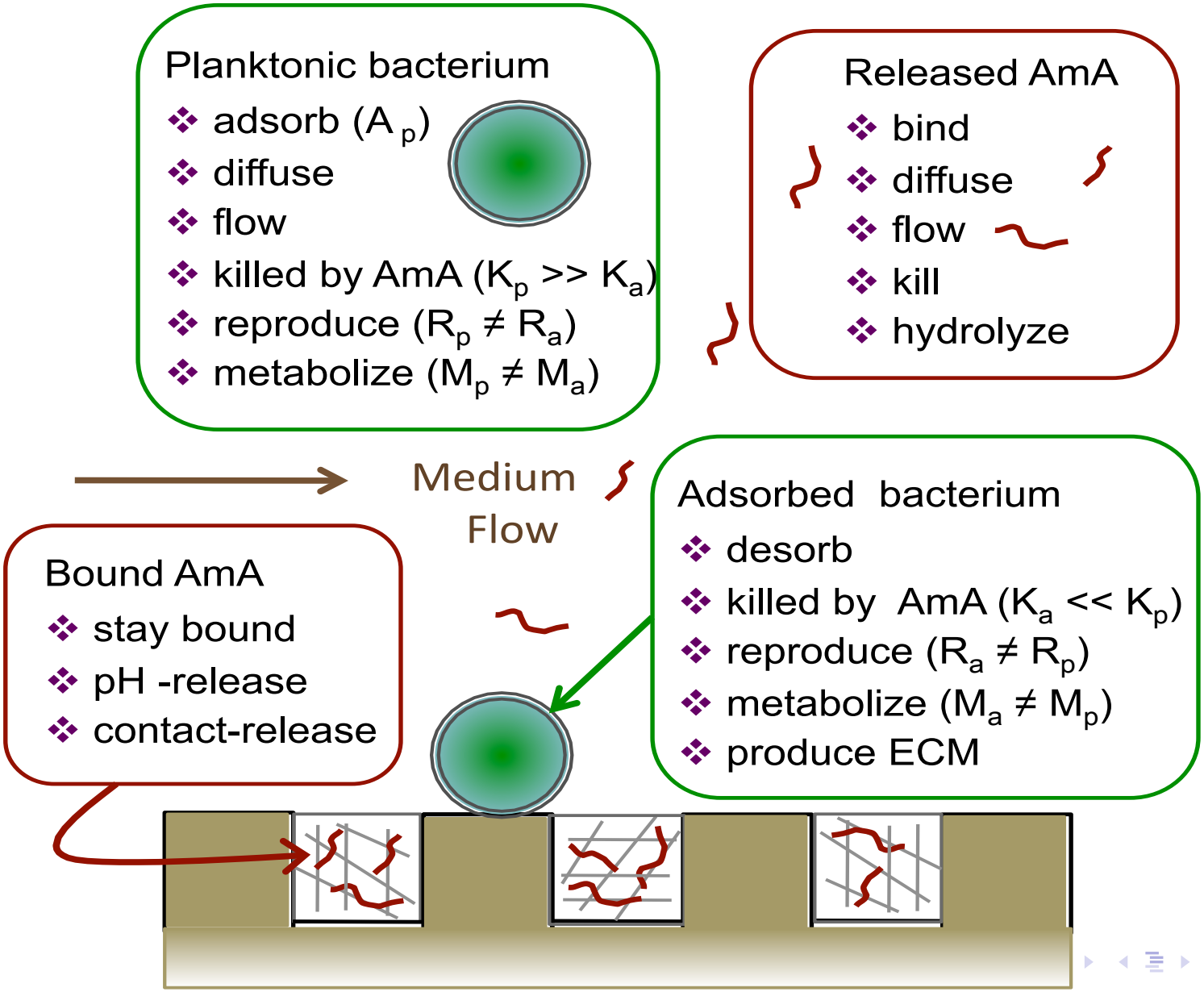
IBM Programming Languages Day
September 23, 2013

Motivation
Towards Antibacterial Surfaces for Medical Implants



Grit-blasted Ti6Al4V used in orthopedic implants promotes osteoblast adhesion/spreading (fluorescence image) but also enhances staphylococcal colonization (SEM inset). After Wu, Libera et al.

Motivation
Towards Multifunctional Antibacterial Surfaces



Computational Modeling: What we DO and DON'T

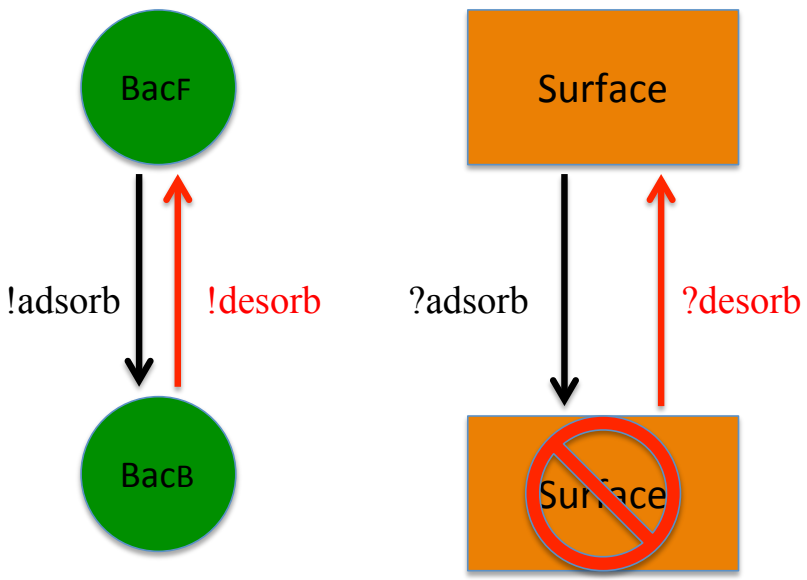
- **We model interactions/behavior.**
  - Bacteria is killed by AmA.
  - Bacteria alters local pH.
  - pH change causes release of AmA.
  - ...

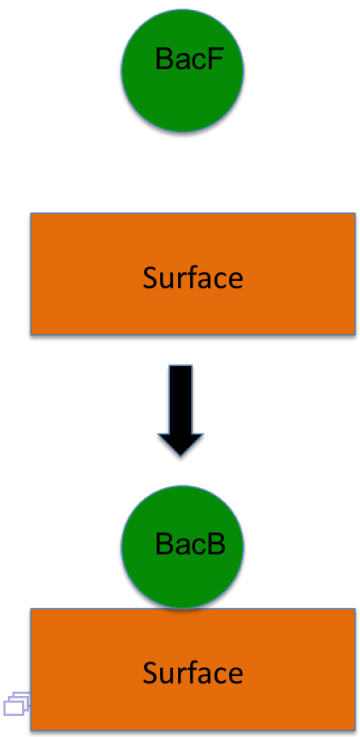
Computational Modeling: What we DO and DON'T

- **We model interactions/behavior.**
- **We use concurrency, stochasticity, 3D space.**
  - Bacteria-biomaterials interactions are highly concurrent.
  - Wet-lab experiments are stochastic.
  - 3D space is essential to bacteria-materials interactions modeling. *A Biological Landscape* (BioScape)

Computational Modeling: What we DO and DON'T

- **We model interactions/behavior.**
- **We use concurrency, stochasticity, 3D space.**
- **We use process algebras.**
  - Stochastic π-calculus
  - Process algebras are formal languages where multiple objects with different behavioral attributes can interact with each other and dynamically influence overall system development.
  - Send/Receive handshake (!/?)



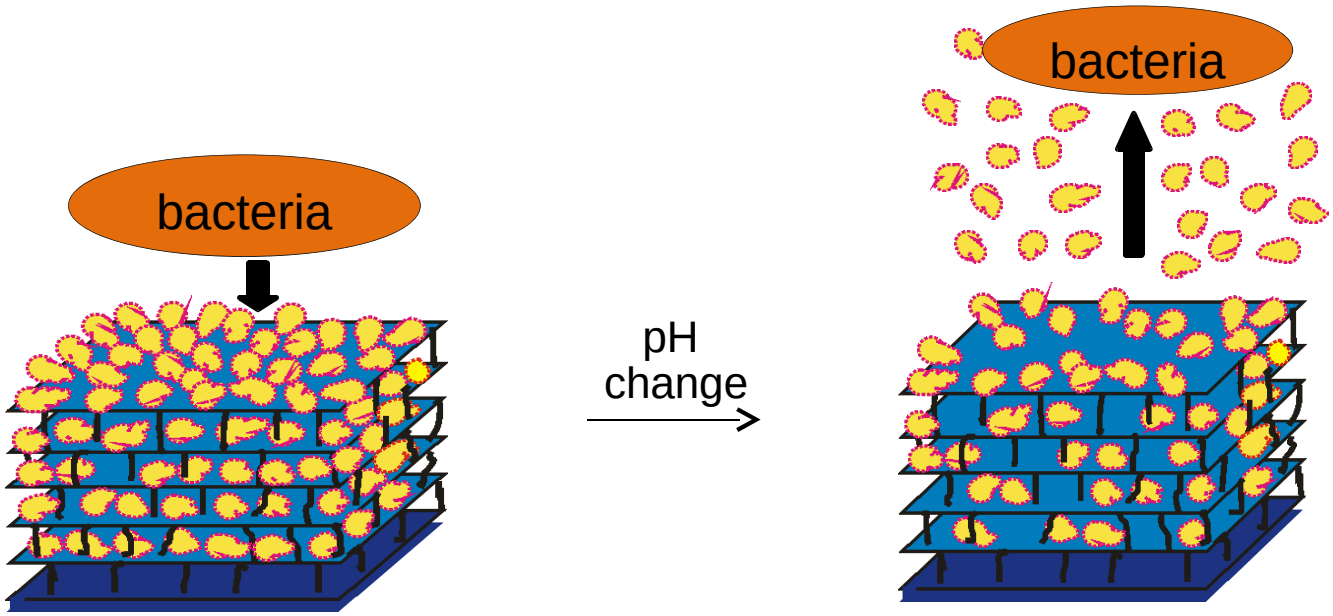


Computational Modeling: What we DO and DON'T

- **We model interactions/behavior.**
- **We use concurrency, stochasticity, 3D space.**
- **We use process algebras.**
- **We don't use differential equations (ODEs).**
  - ODEs are deterministic
  - Cannot handle highly combinatorial complex systems. (one equation for each polymer length or oligomer configuration)

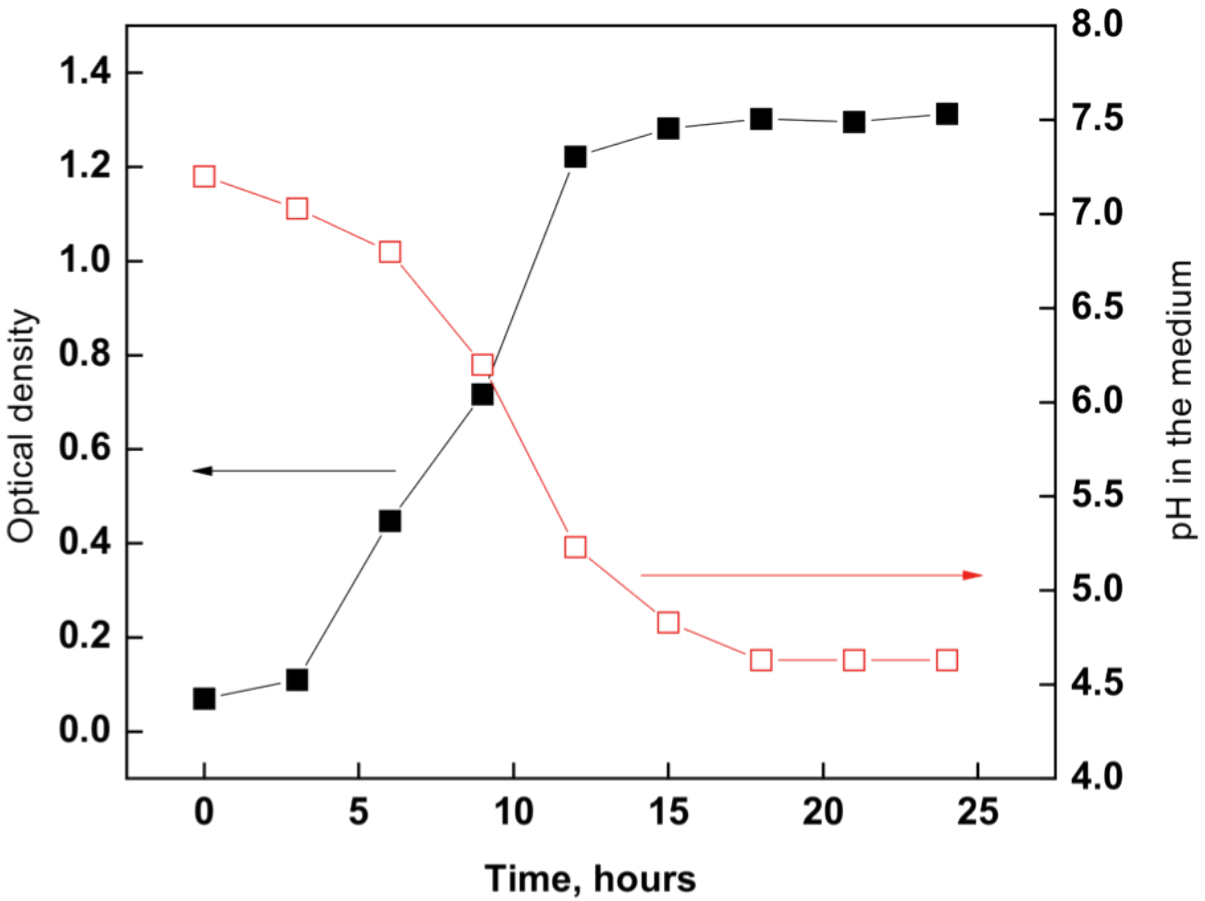
Motivating Example: pH-Triggered Drug Delivery (Sukhishvili)

Goal: develop pH-responsive antibacterial coatings



From Lab Data To Computational Model

Using Sukhishvili's lab data : bacteria vs pH we construct our first model using SPiM (Stochastic Pi Machine), a process algebra programming language.



SPiM Model

```
directive sample 15.0 20
directive plot bac(); molF()

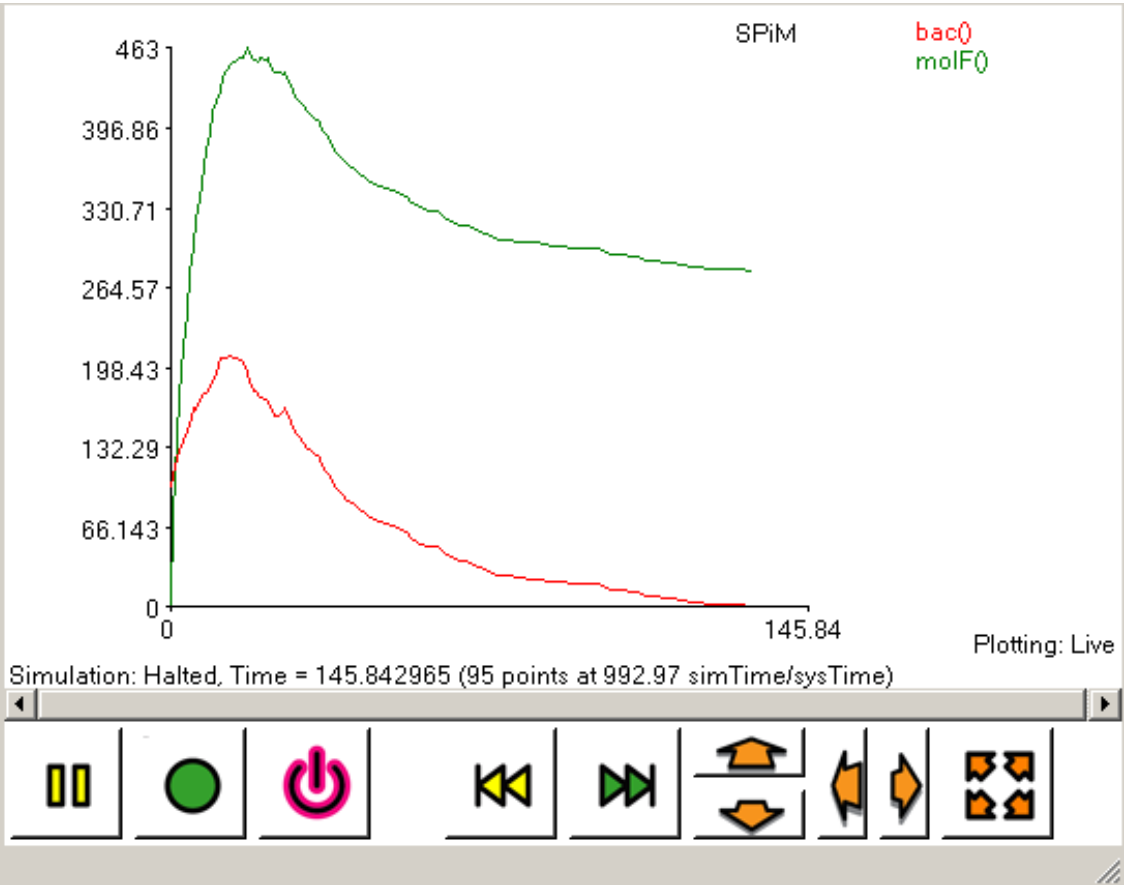
new grow@0.04:chan
new kill@0.0001:chan
new acidic@0.0005:chan
new release@0.04:chan

let bac() =
(
   do ?grow(); (bac()|bac())
   or !acidic; bac()
   or ?kill; ()
)

let molB() = ?release; molF()
and molF() = !kill(); ()

let PH() =
(
   do !release; PH()
   or !grow; PH()
   or ?acidic;()
)


run 800 of molB()
run 100 of bac()
run 3 of PH()
```



We can predict how much antibacterial agent is needed to control bacterial growth.

Can we do better?

```
directive sample 15.0 20
directive plot bac(); molF()

new grow@0.04:chan
new kill@0.0001:chan
new acidic@0.0005:chan
new release@0.04:chan

let bac() =
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let PH() =
(
   do !release; PH()
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run 800 of molB()
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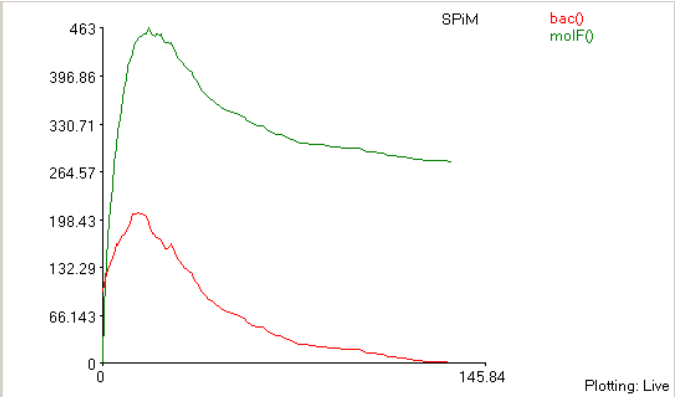

- Can we visualize where bacteria are?
- Do they form clusters?
- Is the antibacterial agent released in the right place?
- Heterogenous mixture or homogenous mixture?

1. Lack spatial attributes: ODEs, SPiM, Kappa, Petri-Nets
2. Limited notion of space: BioAmbients, BioPEPA, StochSim
3. Lack stochasticity: SpacePi, Shape Calculus (BioShape)

BioScape: A New High-Level Modeling and Simulation Language

- Concurrency

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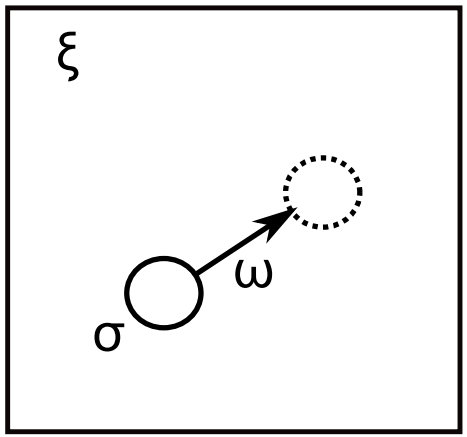
- 3D-Space: each species has 3 new attributes: **shape (σ), step (ω),** and **movement space (ξ)**.



BioScape: A New High-Level Modeling and Simulation Language

- Concurrency
- Stochasticity
- 3D-Space: each species has 3 new attributes: **shape (σ),** **step (ω),** and **movement space (ξ)**.
- Heterogeneous distribution of individual agents (bacteria cannot penetrate hydrogel, for example)

BioScape: A New High-Level Modeling and Simulation Language

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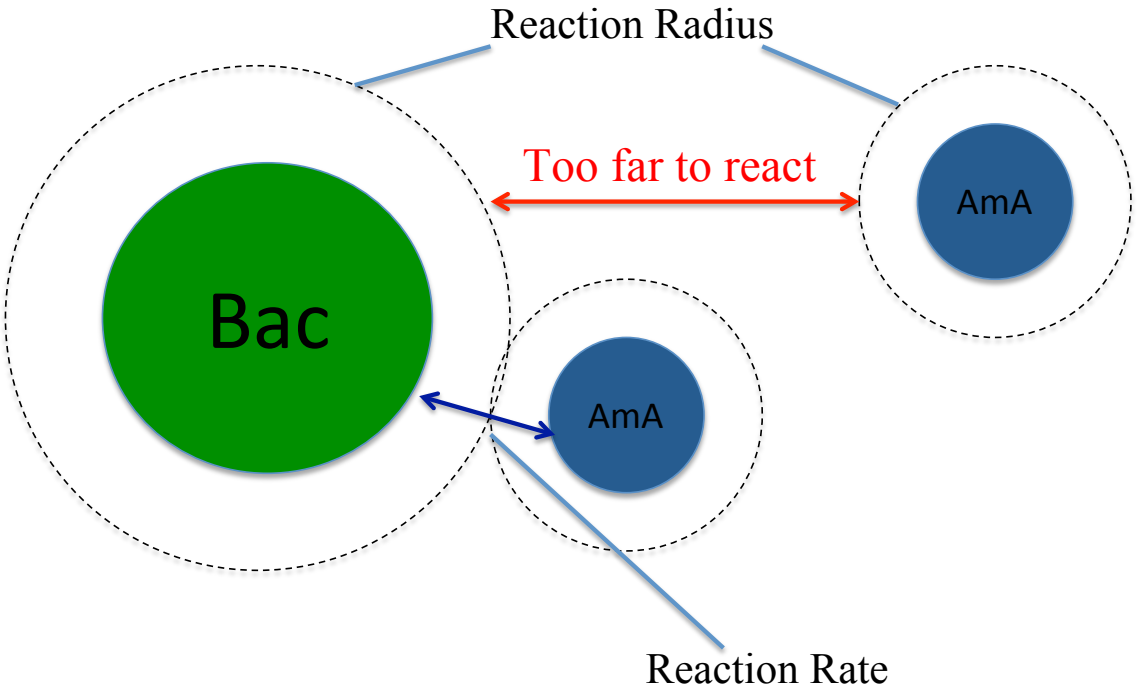
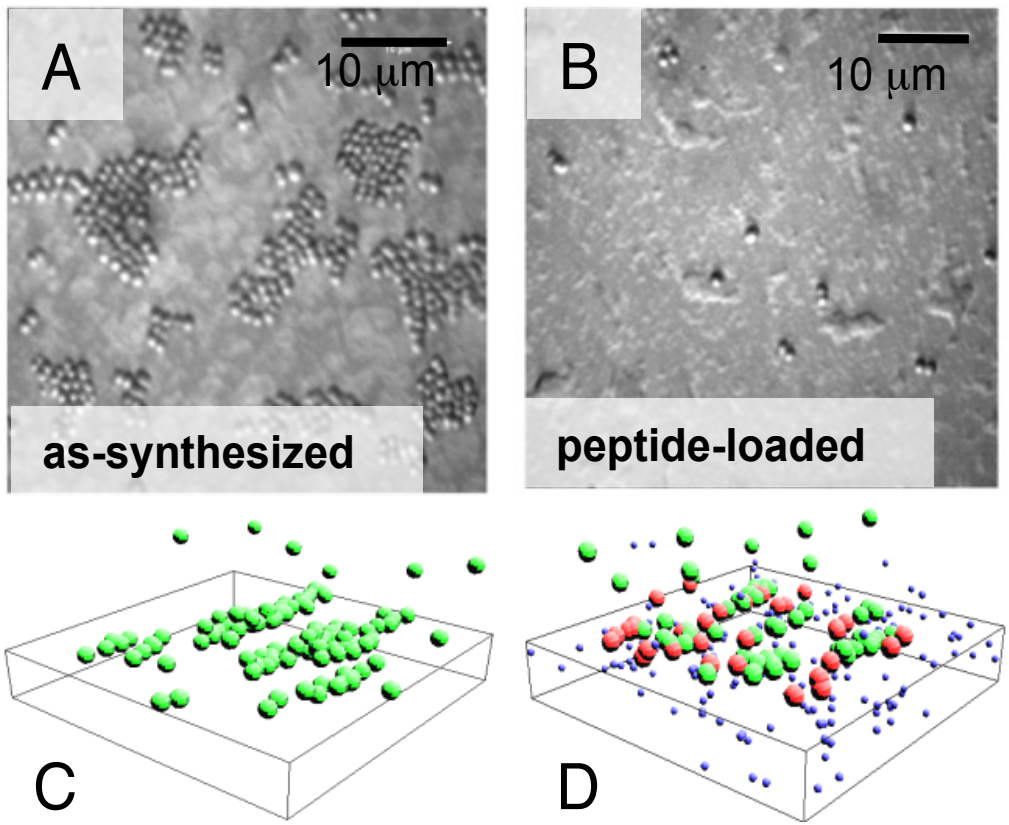
BioScape: A New High-Level Modeling and Simulation Language

- Concurrency
- Stochasticity
- 3D-Space: each species has 3 new attributes: **shape (σ), step (ω),** and **movement space (ξ)**.
- Initial concentrations placed randomly in movement space
- Reaction radius (proximity) and reaction rates



Towards Validation

The following is a validating experiment for our model. Optical micrographs of NJ 9709 S. epidermidis cultured on (A) as-synthesized and (B) L5-loaded (PMAA)10 gels. BioScape simulations with 40 bacteria and (C) an as-synthesized gel film and (D) an L5-loaded gel film. Live bacteria are green, dead bacteria are red, and L5 molecules are small blue dots.

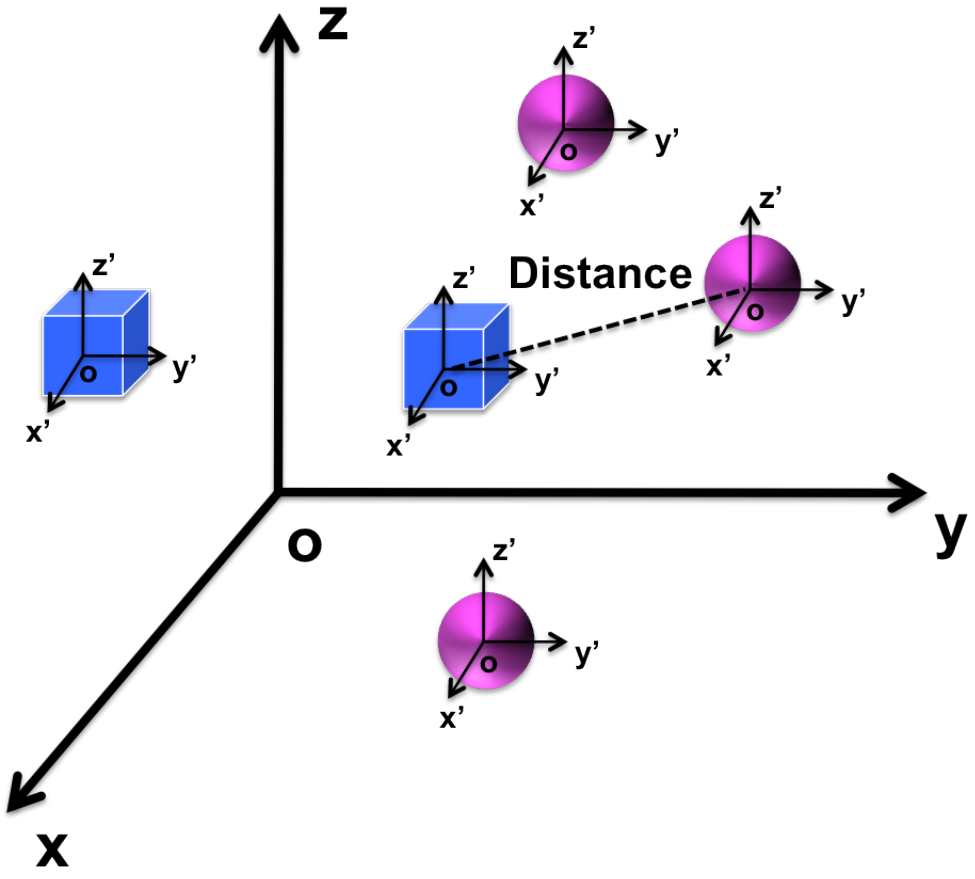


Syntax

$P, Q ::= (\nu x@\mathtt{r}, \mathtt{rad}).P$		Restriction
	$P \mid Q$	Parallel Composition
	M	Heterogeneous Choice
	$X(x)$	Call
$M ::= \mathbf{0}$		Empty Process
	$\pi.P + M$	Choice
$\pi ::= \mathtt{delay@r}$		Delay
	$?x(y) \mid !x(y)$	Input/Output
	$\mathtt{mov}$	Random Movement
$D ::= \emptyset$		Empty
	$D, X(x)@\xi, \omega, \sigma = P$	Definition
$E ::= \emptyset$		Empty
	$E, x@\mathtt{r}, \mathtt{rad}$	Channel Declaration

Semantic Process

- A Process needs to be placed in 3D space



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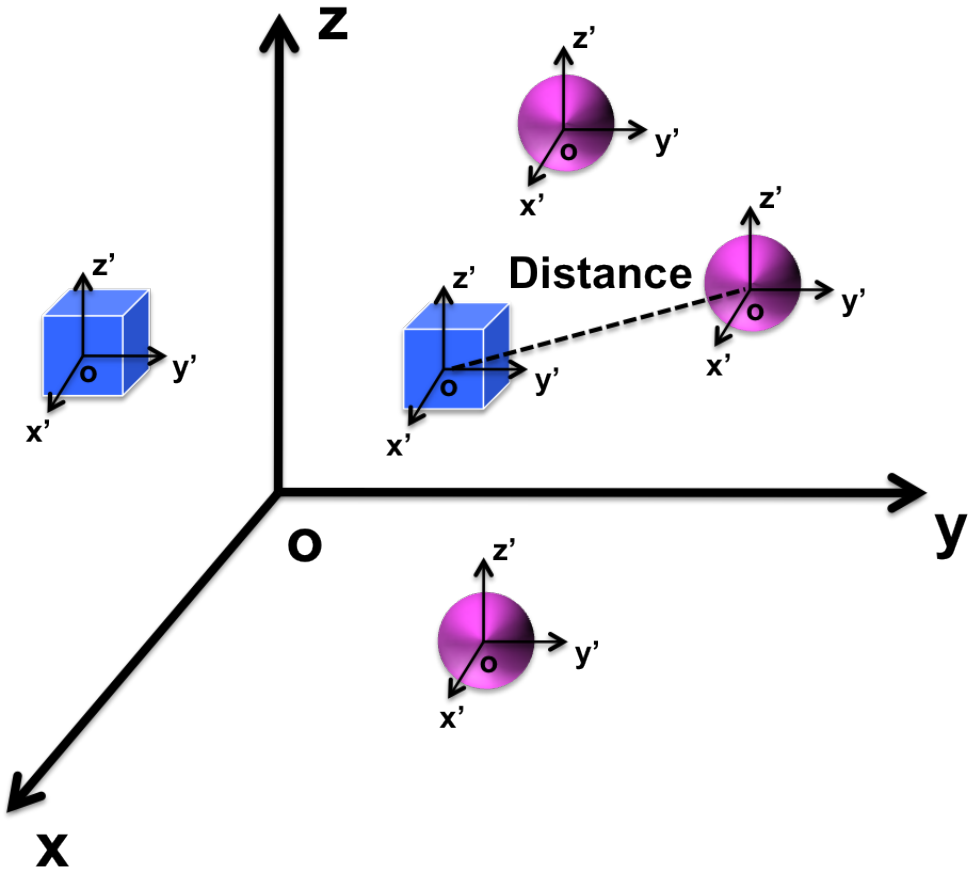

-
  - A located process $\{P\}_\mu$
  - μ local affine map.

Semantic Process

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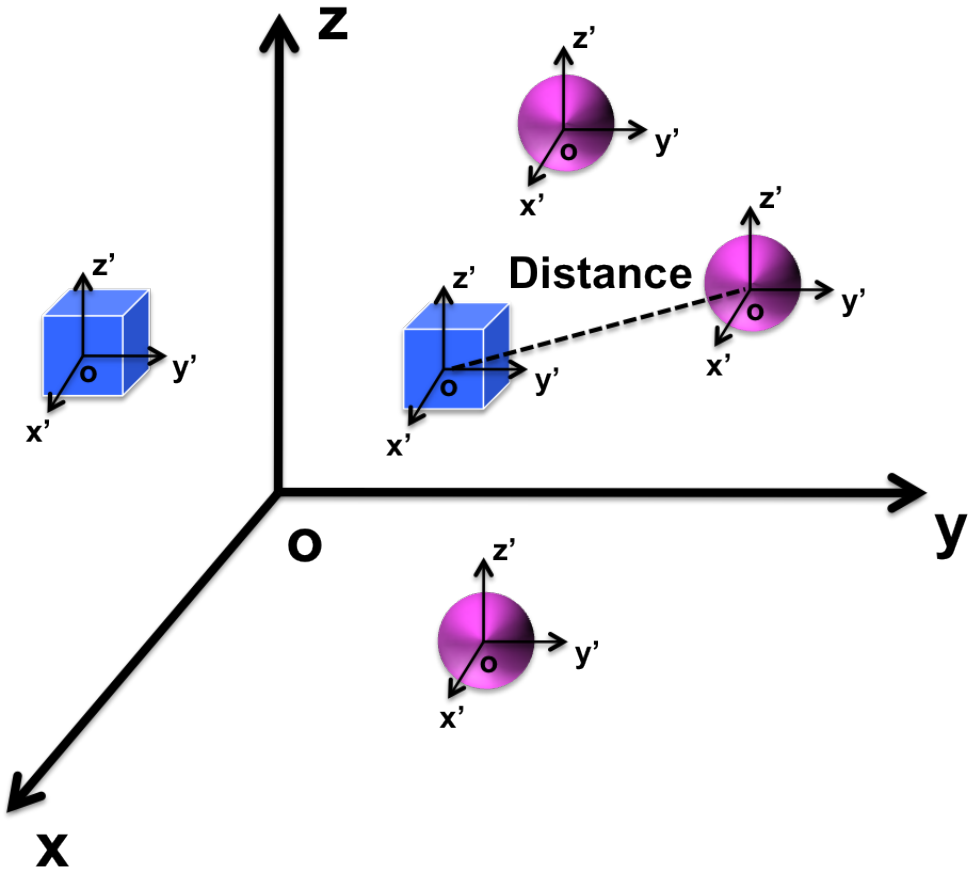

-
  - A located process $\{P\}_\mu$
  - μ local affine map.
- Move does not compete with send or receive (π) and there is no stochastic rate for Move.

Operational Semantics

MOVE

$$\frac{\mu' = \texttt{translate}(\omega, \mu, r) \quad \mu'(\sigma) \subseteq \xi \quad X(x)@\xi, \omega, \sigma = P \in D}{E \vdash \{\texttt{mov}.X(y) + M\}_{\mu} \rightarrow \{X(y)\}_{\mu'}}$$

DELAY

$$\frac{}{E \vdash \{delay@\texttt{r}.P + M\}_{\mu} \rightarrow_{\texttt{r}} \{P\}_{\mu}}$$

INTERACTION

$$\frac{\texttt{dis}(\mu, \mu') \leq \texttt{rad}}{E, x@\texttt{r}, \texttt{rad} \vdash \{!x(y).P + M\}_{\mu} \mid \{?x(z).Q + N\}_{\mu'} \rightarrow_{\texttt{r}} \{P\}_{\mu} \mid \{Q[y/z]\}_{\mu'}}$$

Adriana Compagnoni, Vishakha Sharma, Yifei Bao, Matthew Libera, Svetlana Sukhishvili. Philippe Bidinger, Livio Bioglio and Eduardo Bonelli. BioScape: A Modeling and Simulation Language for Bacteria-Materials Interactions. Electronic Notes in Theoretical Computer Science, 293(0):35 - 49, 2013. Proceedings of the Third International Workshop on Interactions Between Computer Science and Biology (CS2Bio'12).

Translation to 3π

Theorem (Soundness)

If $E \vdash_D A \to B$ *or* $E \vdash_D A \to_r B$ *then*

there exists a set of 3π *processes* S *such that*

$\|A\|^{SPA}_{E;D;r\mathcal{A}} \xrightarrow{*} S$ *and* $S \equiv \|B\|^{SPA}_{E;D;r}$ *for some number* r.

3π does not allow reduction under $+$, therefore, we translate branches in BioScape into sets of processes in 3π.

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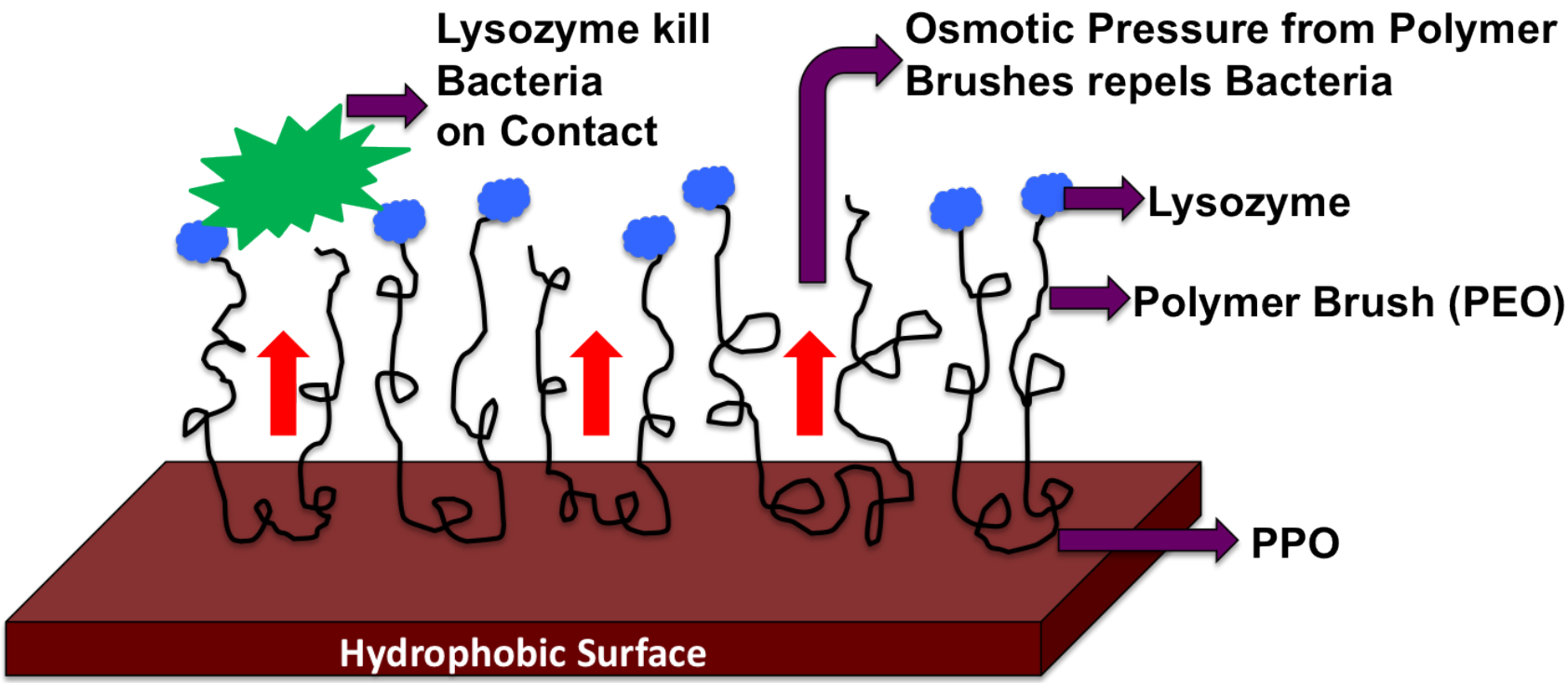
Computational Model of Bifunctional Polymers for Surface Coating

1. Goal: Developing biomaterials that minimize bacterial colonization

Computational Model of Bifunctional Polymers for Surface Coating

1. Goal: Developing biomaterials that minimize bacterial colonization
2. Proposal: Building Computational Model to reduce number of experiments and predict behavior

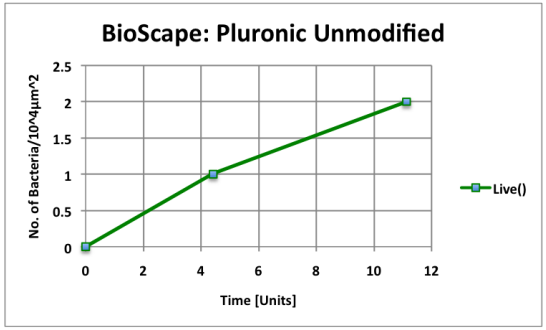
Case Study: From Modeling to Validation and Prediction

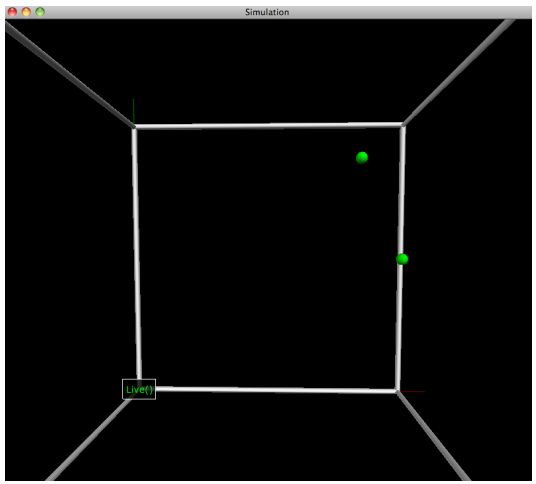


Dr. Henk J. Busscher's group at University Medical Center Groningen, The Netherlands

Adhesion Phase

Training Data





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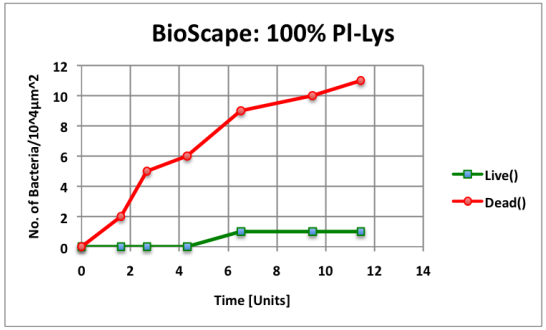
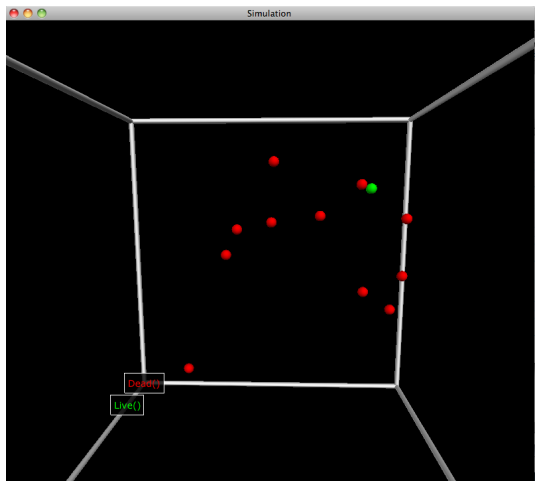
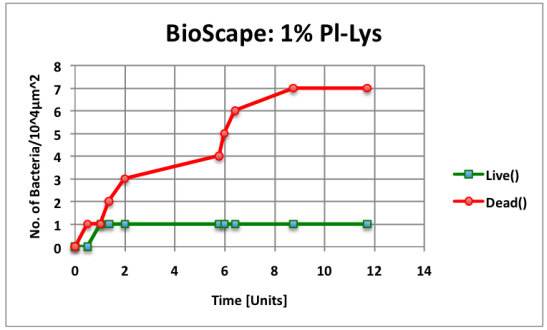
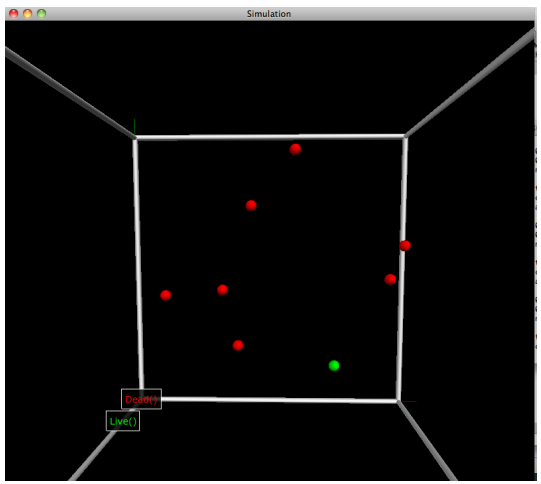




Validation





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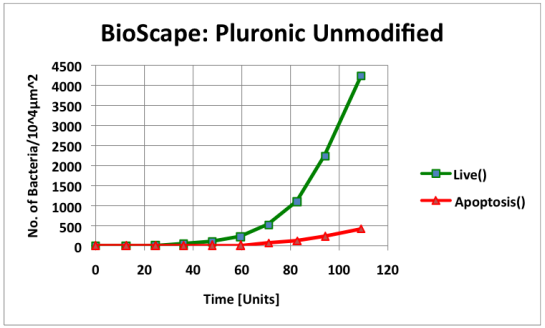
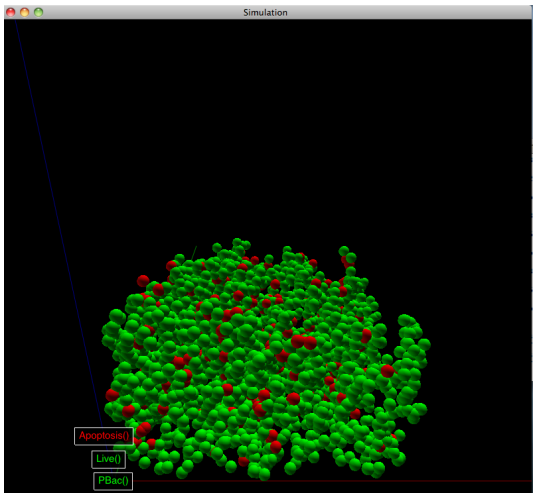
Growth Phase

Training Data





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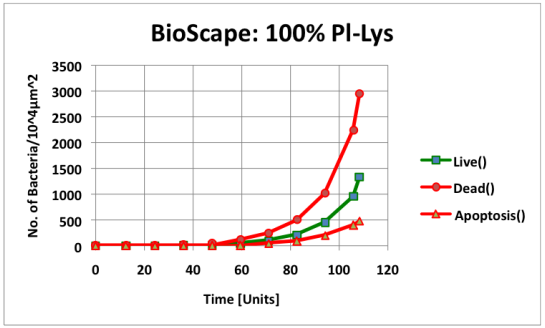

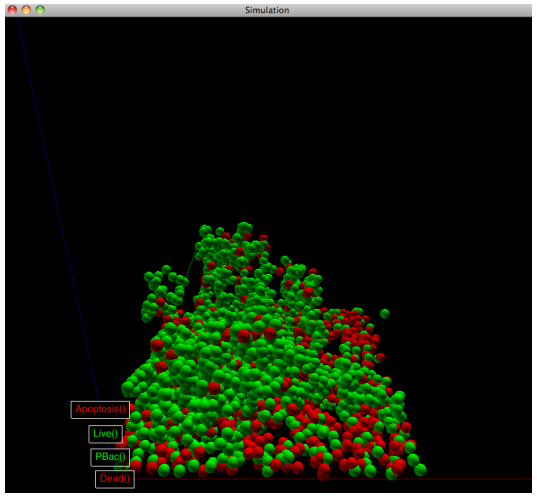

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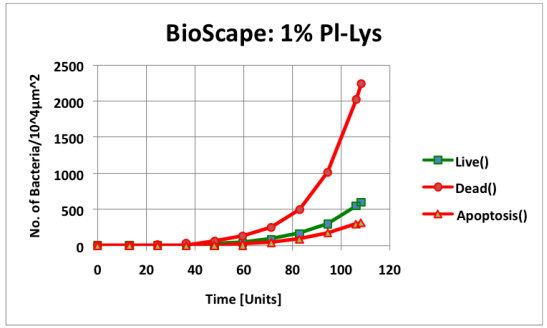

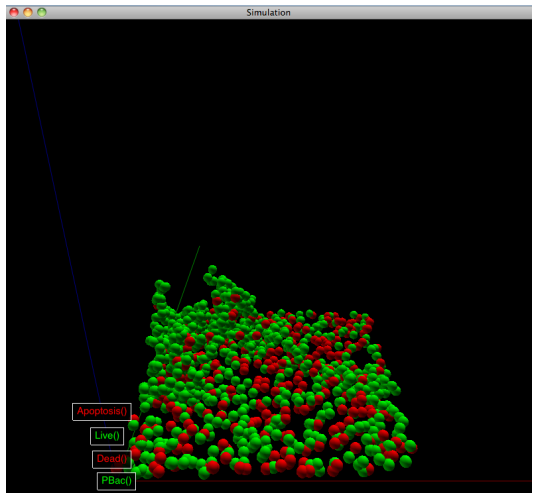

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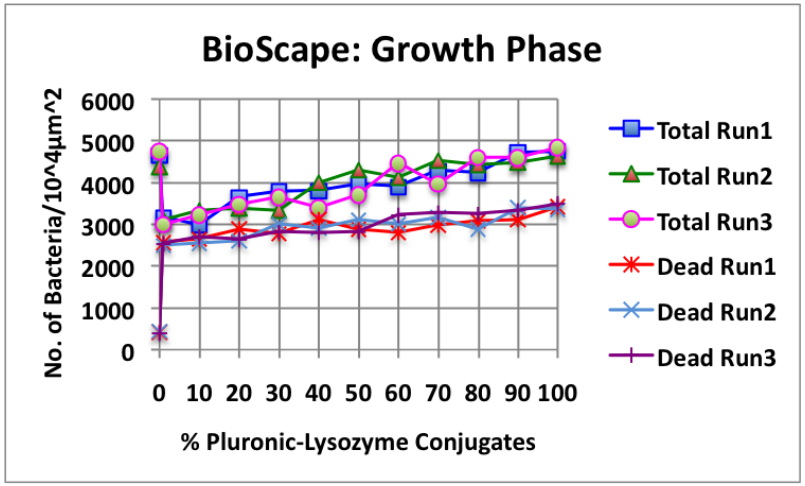
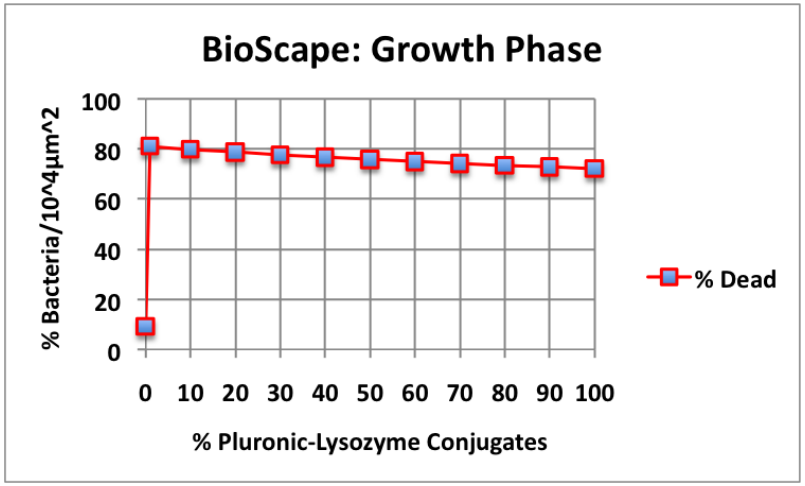
Predictions of the Computational Model

Less is better





Our model predicts that between 1 and 10% of conjugation in the initial concentration yields the minimal amount of bacteria with the maximal percentage of dead bacteria.

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Parallel BioScape: A Stochastic and Parallel Language for Mobile and Spatial Interactions

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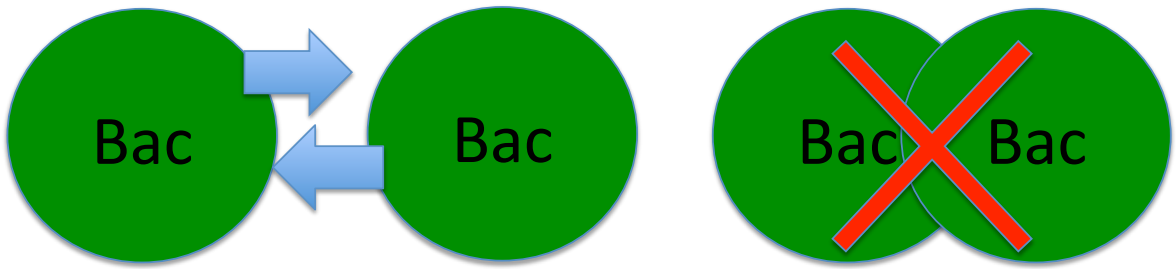
- Parallel Movement: Control on spatial overlapping



Parallel BioScape: A Stochastic and Parallel Language for Mobile and Spatial Interactions

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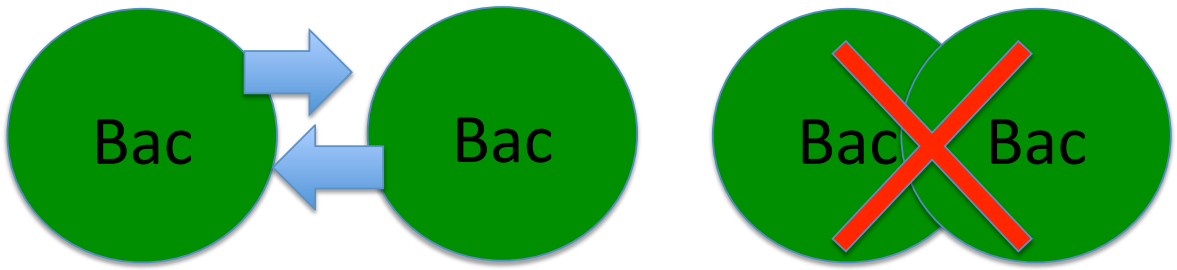
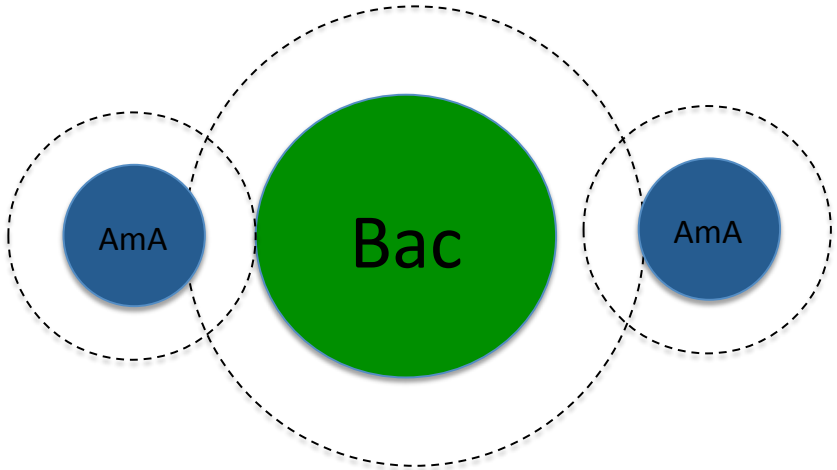


- Parallel Communications: Control on communication conflicts



Challenges

Parallel semantics will execute all available reactions, not just one instance of one reaction.

- **How do we advance the simulation clock?**

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- **Solution:** Timed Configurations
  Annotating each product of a reaction with a timer indicating how long that reaction will take.

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- **How do we advance the simulation clock?**
- **Solution:** Timed Configurations
  Annotating each product of a reaction with a timer indicating how long that reaction will take.
- **Example:** If $Cell \rightarrow_{30} Cell \mid Cell$ means that a *Cell* takes 30 minutes to split, through mitosis, into two daughter cells, then we will annotate the two daughter cells as $\{\!\{Cell\}\!\}^{30}$ and $\{\!\{Cell\}\!\}^{30}$. As time lapses, the timer will be reduced, and when reaching $\{\!\{Cell\}\!\}^{0}$, both cells will be available for new reactions.

Parallel Operational Semantics

MOVEMENTS

$$\frac{F_i \to G_i \quad (1 \le i \le p) \qquad C[\underline{G_1}] \cdots [\underline{G_p}]\ \mathrm{OK}_{mv}}{C[F_1] \cdots [F_p] \rightarrowtail C[G_1] \cdots [G_p]}$$

STOCHASTIC REDUCTIONS

$$\frac{\mathtt{restr}(C) \vdash A_i \xrightarrow{\mathtt{r}_i} B_i \qquad n_i = \tau(\mathtt{r}_i, C_i[A_i]) \quad (1 \le i \le p) \qquad C[C_1[\underline{B_1}]] \cdots [C_p[\underline{B_p}]]\ \mathrm{OK}_{st}}{C[C_1[A_1]] \cdots [C_p[A_p]] \dashrightarrow C[C_1[\{\!\{B_1\}\!\}^{n_1}]] \cdots [C_p[\{\!\{B_p\}\!\}^{n_p}]]}$$

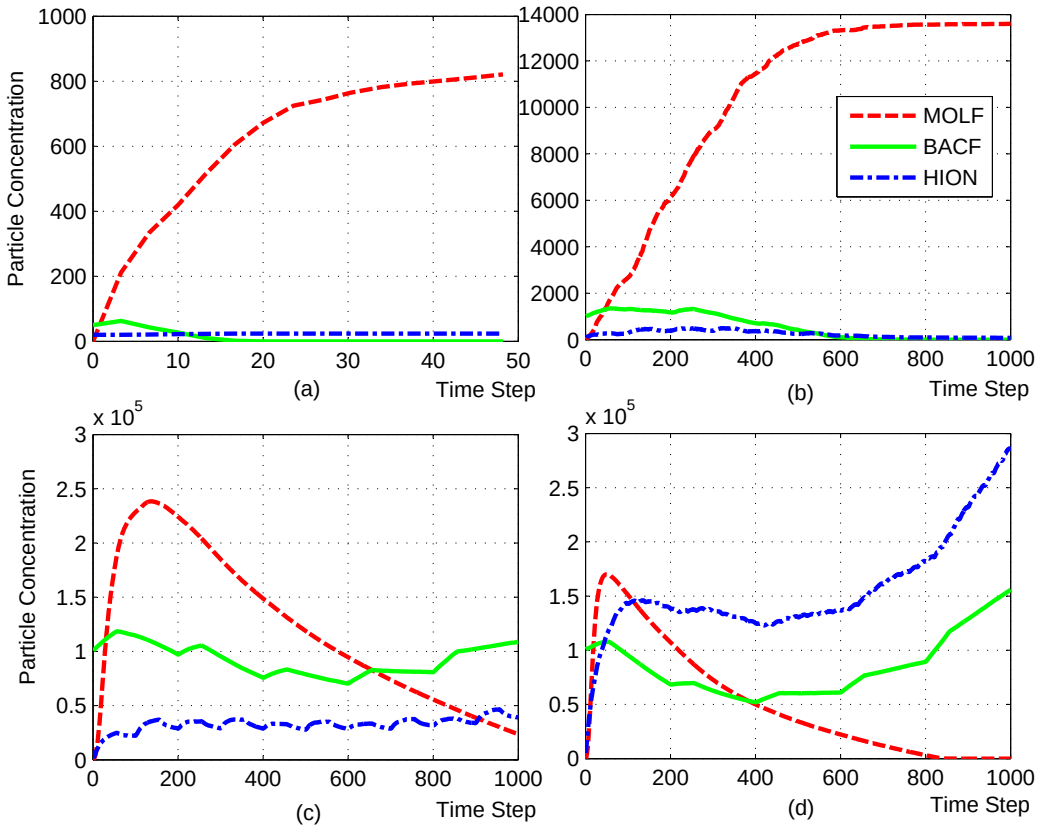
TIMED DELAY

$$\frac{n = min\{n_i \mid 1 \le i \le p\} \quad C \text{ is timed}}{C[\{\!\{A_1\}\!\}^{n_1}] \cdots [\{\!\{A_p\}\!\}^{n_p}] \rightsquigarrow C[\{\!\{A_1\}\!\}^{n_1-n}] \cdots [\{\!\{A_p\}\!\}^{n_p-n}]}$$

CONFIGURATION EVOLUTION

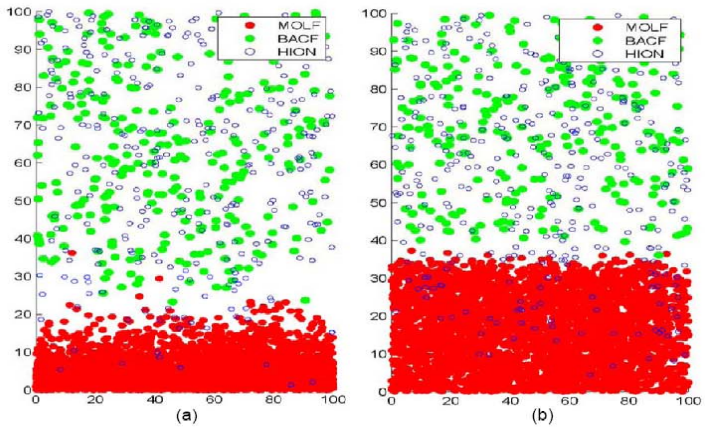
$$\frac{F \rightarrowtail F_1 \dashrightarrow F_2 \rightsquigarrow F'}{F \to F'}$$

Particle concentration (a)CPU simulation, (b)Comparable GPU simulation, (c,d)GPU-BioScape distribution for different settings.



Jie Li, Vishakha Sharma, Narayan Ganesan, and Adriana Compagnoni. Simulation and Study of Large- Scale Bacteria-Materials Interactions via BioScape Enabled by GPUs. In Proceedings of ACM-BCB 2012, Pages 610-612.

(a,b)Particle distribution at time 10 and 100, (c)Performance w.r.t total number of particles



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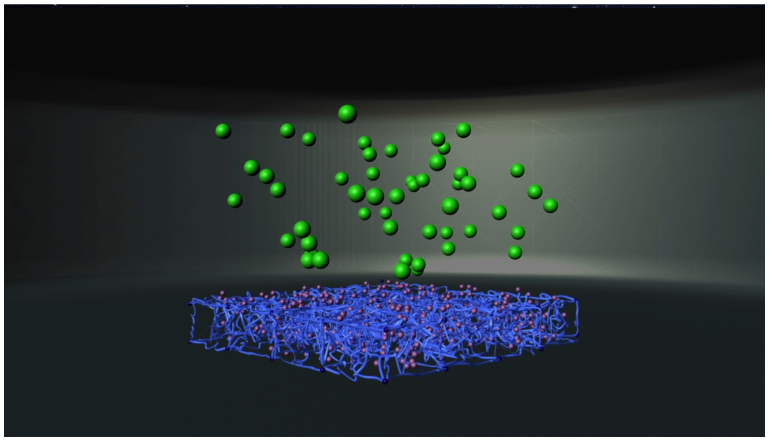
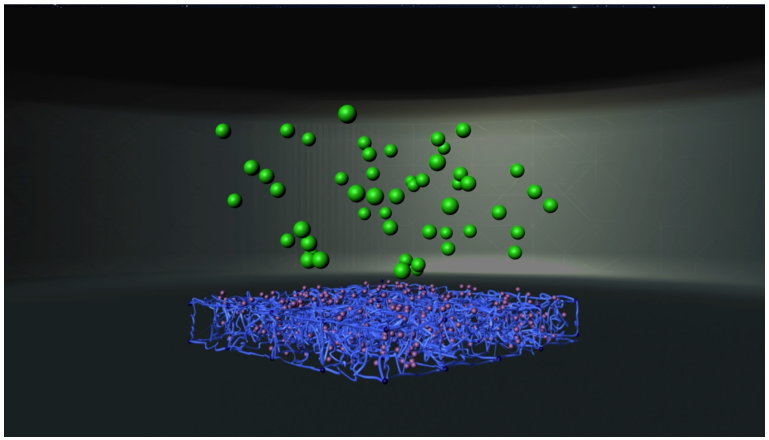


- We defined BioScape
  $X(x : T) = M^{\xi,\omega,\sigma}$
  entities have a space where they can be ξ, a diffusion rate ω, and a shape σ.



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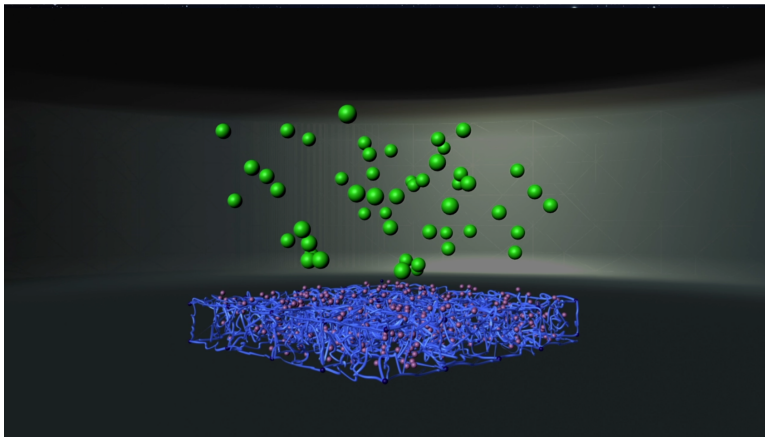

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- But the programmer has **no control** over the **exact position** or even **relative position** of entities.

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Issues:

- We cannot describe complex structures: polymers/oligomers/membranes
- We cannot describe pre-existing/reactive environment - video games/ antibacterial surfaces
- If we want to start in a pre existing world that has not been stochastically assembled but designed instead, we need to extend the language with a *programmable location for each entity*.

$P, Q ::=$	$\mathbf{0}$	Empty Process
	$\mid X(\delta)_\delta$	Located Entity Instance
	$\mid P \mid Q$	Parallel Composition
	$\mid (\nu a@\mathtt{r}, \mathtt{rad} : \mathtt{chan}\{T\}).P$	Restriction
$M ::=$	$\pi.P\ [+ M]$	Choice of Prefixed Process
$\pi ::=$	$\mathtt{delay@r}$	Delay
	$\mid\ !u(\delta)$	Output
	$\mid\ ?u(x)$	Input
	$\mid\ \mathtt{mov}$	Move

Adriana Compagnoni, Paola Giannini, Catherine Kim, Matthew Milideo, Vishakha Sharma A Calculus of Located Entities. 9th International Workshop on Developments in Computational Models (DCM) 2013. To appear.

$$
\begin{array}{lr}
u ::= a \mid b \mid \cdots \mid x \mid y \mid \cdots & \text{Identifiers} \\
\delta ::= u \mid \mathtt{c} \mid \mathtt{this} \mid \delta_1, \ldots, \delta_n \mid () \mid \delta.i \mid \mathtt{op}(\delta) & \text{Expressions} \\
v ::= a \mid b \mid \cdots \mid \mathtt{c} \mid () \mid v_1, \ldots, v_n & \text{Values} \\
T ::= \mathtt{chan}\{T\} \mid \mathtt{fl} \mid T_1 * \cdots * T_n \mid \top & \text{Types} \\
D ::= \emptyset \mid D, X(x : T) = M^{\xi,\omega,\sigma} \quad \mathtt{FV}(M) \subseteq \overline{x} & \text{Definitions} \\
E ::= \emptyset \mid E, a@\mathtt{r}, \mathtt{rad} : \mathtt{chan}\{T\} & \text{Declarations} \\
\Gamma ::= \emptyset \mid \Gamma, X{:}T \mid \Gamma, u{:}T & \text{Environment}
\end{array}
$$

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```
Bac() =
do mov.Bac()_(this,0)
or delay@0.005.(Bac()_(this,0) | HIon()_(this,rB+rH))
or ...
```

Figure: (a) Random Translation

```
Bac() = ... max-size ...
do delay@0.005.(Bac()_(this.1,0,1) | HIon()_(this.1,rB+rH,1))
or delay@0.2.(Bac()_(this.1,rB,0.5) | Bac()_(this.1,rB,0.5))
or mov.Bac()_(this.1,0,1.1)
or .....
```

Figure: (b) Scaling

Conclusions and Future Work

Conclusions:

1. We define BioScape, a high-level modeling and simulation language for the stochastic simulation of biological and biomaterials processes.
2. We compile BioScape into 3π, and prove the soundness of the translation.
3. We visualize biofilm formation.
4. We construct and validate the stochastic computational model for antibacterial surfaces.
5. We define BioScape with a fully parallel semantics in order to model larger and more realistic systems (GPU architectures).
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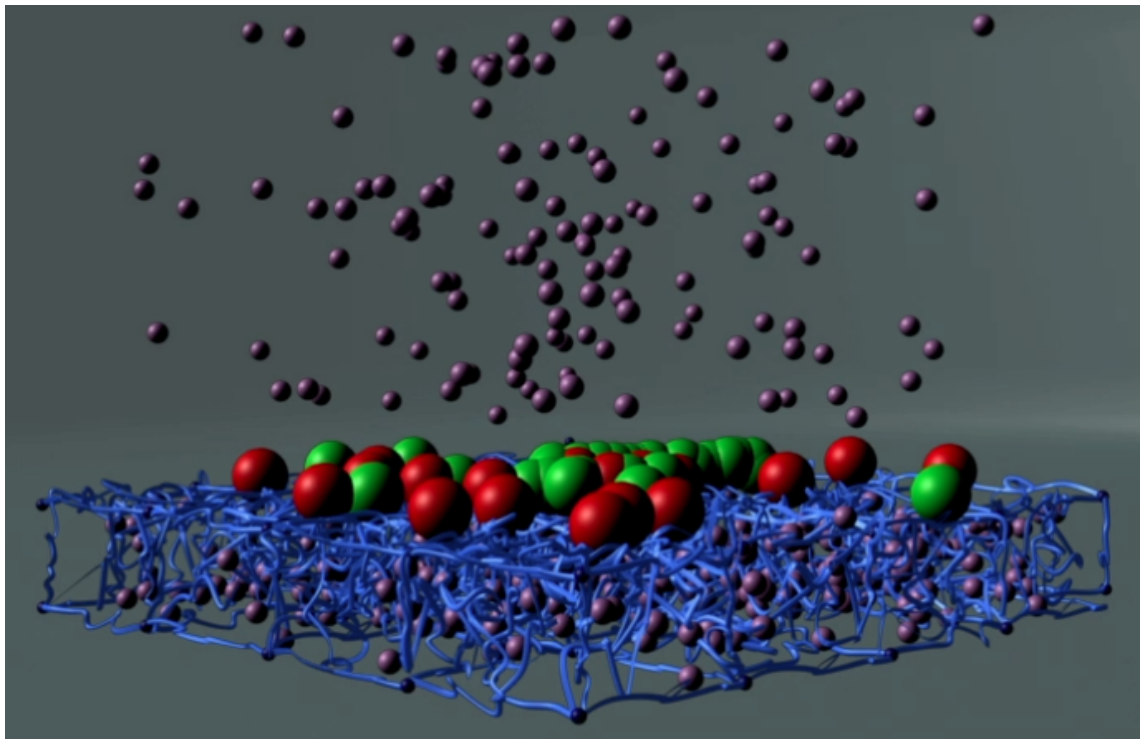
Future work:

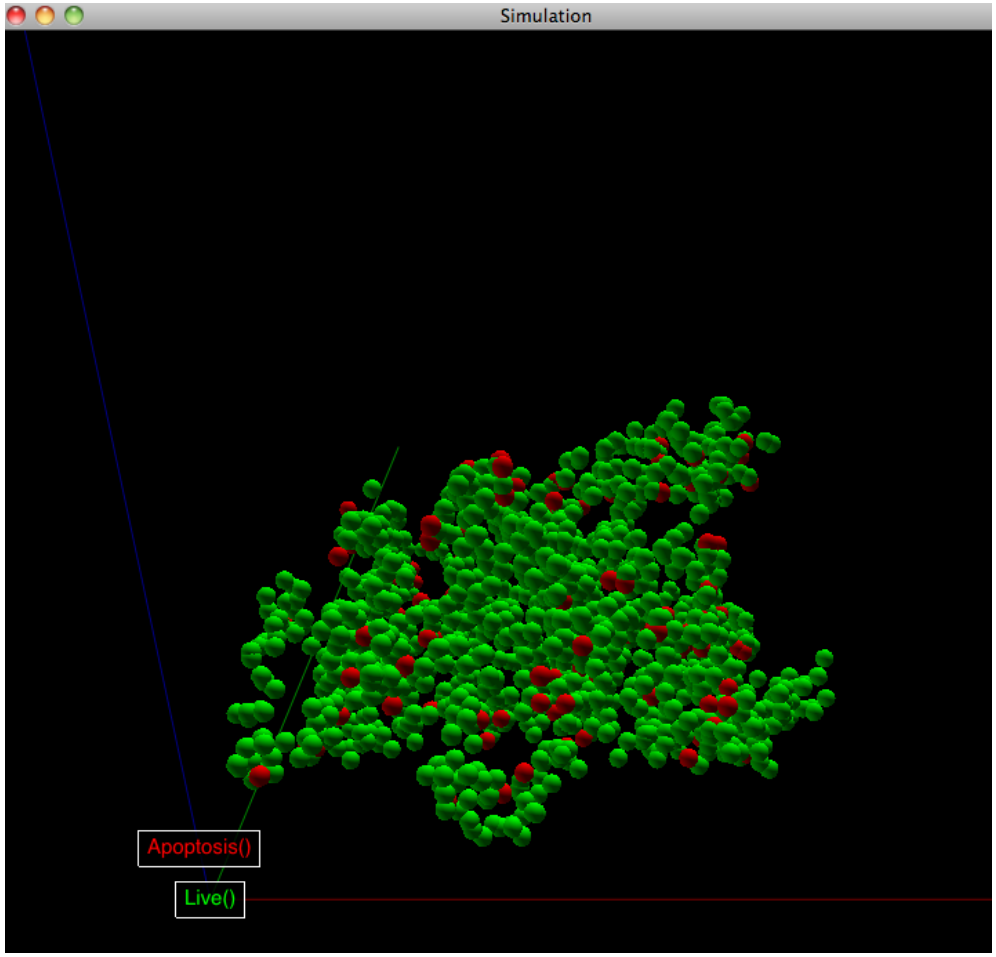
1. Build a framework based on BioScape^L for the computationally assisted development of antibacterial surfaces
2. Study adenoviral traffic in healthy/cancerous eukaryotic cells.

Simulation Results

Bio-triggered drug delivery system for infection-resistant medical implants



Simulation Results
Bacterial Growth on Unmodified Pluronic Surface



Publications

1. Adriana Compagnoni, Vishakha Sharma, Matthew Libera, Svetlana Sukhishvili, Philippe Bidinger, Livio Bioglio, Eduardo Bonelli. BioScape: A High-Level Modeling and Simulation Language. Theoretical Computer Science (TCS) 2013. Submitted.
2. Vishakha Sharma, Adriana Compagnoni, Matthew Libera, Agnieszka K. Muszanska, Henk J. Busscher and Henny C. van der Mei. Simulating Anti-adhesive and Antibacterial Bifunctional Polymers for Surface Coating using BioScape. ACM Conference on Bioinformatics, Computational Biology and Biomedical Informatics, 2013. September 22 - 25, Washington, DC. To appear.
3. Adriana Compagnoni, Paola Giannini, Catherine Kim, Matthew Milideo, Vishakha Sharma A Calculus of Located Entities. 9th International Workshop on Developments in Computational Models (DCM) 2013. To appear.
4. Vishakha Sharma and Adriana Compagnoni. Computational and Mathematical Models of the JAK-STAT Signal Transduction Pathway. To appear in Proceedings of SCSC 2013. July 7 - 10, Toronto, Canada.
5. Adriana Compagnoni, Vishakha Sharma, Yifei Bao, Matthew Libera, Svetlana Sukhishvili. Philippe Bidinger, Livio Bioglio and Eduardo Bonelli. BioScape: A Modeling and Simulation Language for Bacteria-Materials Interactions. Electronic Notes in Theoretical Computer Science, 293(0):35 - 49, 2013. Proceedings of the Third International Workshop on Interactions Between Computer Science and Biology (CS2Bio'12).
6. Adriana Compagnoni, Mariangiola Dezani-Ciancaglini, Paola Giannini, Karin Sauer, Vishakha Sharma, Angelo Troina. Parallel BioScape: A Stochastic and Parallel Language for Mobile and Spatial Interactions. In Proceedings Sixth Workshop on Membrane Computing and Biologically Inspired Process Calculi. 8th September 2012, Newcastle, UK. (MeCBIC 2012). In Electronic Proceedings in Theoretical Computer Science, Volume 100 Issue 7, Pages 101-106, 2012.
7. Jie Li, Vishakha Sharma, Narayan Ganesan, and Adriana Compagnoni. Simulation and Study of Large-Scale Bacteria-Materials Interactions via BioScape Enabled by GPUs. In Proceedings of ACM-BCB 2012, Pages 610-612.

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  - Narayan Ganesan, Department of Electrical and Computer Engineering
  - Matthew Libera, Department of Chemical Engineering and Materials Science
  - Svetlana A. Sukhishvili, Department of Chemistry, Chemical Biology and Biomedical Engineering
- External Collaborators
  - Philippe Bidinger (VERIMAG)
  - Livio Bioglio (University of Turin)
  - Eduardo Bonelli (University of Quilmes)
  - Henk Busscher (UMCG)
  - Mariangiola Dezani-Ciancaglini (University of Turin)
  - Paola Giannini (University of Piemonte Orientale)
  - Henny van der Mei (UMCG)
  - Karin Sauer (SUNY at Binghamton)
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Thank You!