Lost in Translation from Genes to Organisms

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The Evo-Devo Challenge

**Macroevolution**
- Faunas
- Species
- Ecological interactions

**Microevolution**
- Populations
- Molecular interactions

**Development**
- Individuals
Tooth Evo-Devo

*Evo*
- food and ecology
- diversity of shapes
- fossil record

*Devo*
- shape changes after formation only by wear
Tribosphenic (no hypocone)
Quadritubercular (hypocone)
Bilophodont (hypocone + shearing crests)

Teeth

Crown types

2100 2200 2202
Teeth

- Tribosphenic (no hypocone)
- Quadritubercular (hypocone)
- Bilophodont (hypocone + shearing crests)

Crown types

- 2100
- 2200
- 2202
The hypocone: evolved many times

primates, artiodactyls, perissodactyls, bears, rodents, bats, hedgehogs......over 20 cases
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MAMMALIAN TEETH 1995

From simple networks to...

![Diagram showing the relationship between BMP, Msx1, Msx2, FGF, SHH, p21, and differentiation.]
...to more complex interactions

![Diagram of molecular interactions in mammalian teeth differentiation and proliferation](image-url)
'Secondary enamel knots' present in future cusp tips

Fgf4 in situ (Jernvall et al. 1994)
Geographic Information Systems (GIS)
Secondary enamel knots in Mice and Voles

Development

Coexpression:
- Yellow: Shh + p21 + Lef1 + Fgf4
- Orange: Shh + p21 + Lef1
- Red: Shh + p21

Buccal

1st lower molar

1st lower molar
Gene expression data

Whole-mount *in situ*

**INTENSITY ROUNDDING**
Standardized expression intensities with five steps

**SPATIAL ROUNDDING**
30µm x 30µm squares
Cross-correlations between gene expression patterns and topography

Mouse

- Lef1
- p21
- Fgf4
- Shh

Developmental stage

Mouse:
- E14.5 (0)
- E15 (0)
- E16 (2)
- E17 (4)

Vole:
- E14 (0)
- E15 (0)
- E16 (6)
- E18 (8)
Observing the enamel knots
E14 Shh-gfp reporter mice

Development (days)

1st molar
2nd molar

CULTURING TEETH

tooth
filter support
grid support
media
petri dish
Greentooth
Green Fluorescent Protein (GFP) producing gene (from jellyfish *Aequorea*) in mouse under *Shh* promoter
How does the genotype map onto the tooth shape....
....how many genes to go?
How does the genotype map onto the tooth shape.... ....how many genes to go?

Expression pattern:

<table>
<thead>
<tr>
<th>Expression Pattern</th>
<th>Gene Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium</td>
<td>n = 4, genes = 3</td>
</tr>
<tr>
<td>Enamel knot</td>
<td>n = 7, genes = 6</td>
</tr>
<tr>
<td>Mesenchyme</td>
<td>n = 4, genes = 2</td>
</tr>
</tbody>
</table>

Transcription factor binding sites

A-B distance (bp)

B-C distance (bp)

Heikki Mannila, Aris Gionis, Irma Thesleff
Morphodynamic computational model

\[ \frac{\partial A}{\partial t} = \frac{k_1[A]}{k_2[I] + 1} + k_3 + D_A \nabla^2 [A] \]

Activators

\[ \frac{\partial I}{\partial t} = [A] + D_I \nabla^2 [I] \]

Inhibitors

Epithelial proliferation

Mesenchymal proliferation

\[ R_j(i) = D_j R_m \sum_{k=0}^{k=m(i)} [I]_{ik} \]

\[ R_j(i) = D_j R_m \sum_{k=0}^{k=m(i)} [I]_{ik} + B_j \text{ for } j \in [p, a, b, l] \]

\[ S_j = 1 / \left( \sum_{k=0}^{n(i,j)} \sum_{l=0}^{m(k)} 1 \right) \]

Shape

Mesenchyme

Analysis

p21

etc.

Mesenchymal proliferation

Epithelial proliferation

FGFs

SHH

etc.

Epithelial proliferation

Mesenchymal proliferation

Model construction

Gene network simplification

A

I

BMPs

etc.

Gene network simplification

Morphodynamic simulations

Shape

Activator

Inhibitor

Time

First cusp

Second cusp

Epithelial proliferation

Mesenchymal proliferation

Epithelial proliferation

Mesenchymal proliferation

Shape

Analysis

EK

Epithelium

EK

Mesenchyme

SHAPE

GENE NETWORK
Shape development

Predicted  Observed

Mouse

Vole

Anterior
# Shape development

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vole</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Anterior**
Rate of crown formation

Model iteration
- Predicted
- Observed
- Morphed

Embryonic day
- Mouse
- Vole

Cusps (N)
- 0 (late cap)
- 0 (early cap)

Predicted: Vole and Mouse growth curves.
Observed: Vole and Mouse growth curves with markers.
Morphed: Vole and Mouse growth curves with markers and arrows.
Mathematical modeling suggests that there should be an inhibitor of cusp induction........where?
Inhibiting enamel knots

ectodin (a.k.a.: Sostdc1, USAG1, wise), a BMP antagonist, member of DAN/Cerberus family

Developing (E16)

Erupted

P = Protoconid

P21

wild type

ectodin

M1  M2

0.5mm

1mm
**Inhibiting enamel knots**

*ectodin* (a.k.a.: *Sostdc1*, *USAG1*, *wise*), a BMP antagonist, member of DAN/Cerberus family

Developing (E16) vs. Erupted

**Wild type**

- **ectodin**
- **p21**

**Ectodin** -/-

- **ectodin**
- **p21**

*Science 309, 2067 (2005)*
Time-lapse of simulated mouse tooth development

Shape with inhibitor

Cell shapes

Time-lapse of developing mouse first molar

Time
The Evo-Devo Challenge

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How many ways to the hypocone?
Multiple ways to obtain the hypocone

Fossil teeth

Simulated teeth

For example: Decrease in inhibition of activator ($k_2$) OR increase in lingual growth bias ($B_l$)
Simulated development

Parameter space

Morphospace
Simulated development

Parameter space

Morphospace
Crown type frequency of 4,378,386 simulated teeth

- Tribosphenic
- The hypocone
- Bilophodont
All roads lead to the hypocone?
Crown type diversity and complexity through the Cenozoic in North American ungulates.
Crown type diversity and complexity through the Cenozoic in North American ungulates

Does the developmental likelihood remain unchanged through time?

4,378,386 teeth

Tribosphenic

The hypocone
Crown type diversity and complexity through the Cenozoic in North American ungulates.
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Evolutionary diversity of murine rodents
Digital phenotype storage

Phenotype data mining

Search method development
Shape mining

Cusps

Surface relief

Elongation

Patch complexity

Ilja Pljusnin
Shape mining pipeline

Hydromys

122 patches

Mallomys

241 patches

(a) Acquiring data
(b) Preprocessing
(d) Obtaining features
(e) Choosing classifiers
(f) Searching
(g) {classifier, best subset}
(i) Interpreting

1. patch complexity
2. surface complexity
3. elongation
4. local window maxima
5. local window minima
6. shape distribution

1. Naive Bayes
2. Tree
3. Nearest Neighbor

Best first search using classifier as validator
Patch complexity of cheek teeth

wild cat  
*Felis silvestris*

37 patches

giant panda  
*Ailuropoda melanoleuca*

257 patches

water rat  
*Hydromys chrysogaster*

122 patches

woolly rat  
*Mallomys rotschildi*

241 patches

How different are cats and mice?

Alistair Evans, Gregory Wilson
Patch complexity of cheek teeth

Carnivoran diet

Animals

Plants

Rodent diet

Animals

Plants

Carnivore

Plant-omnivore

Herbivore

Hypercarnivore

Animal-omnivore

Herbivore

Hypercarnivore

Animal-omnivore

Herbivore

Ailuropoda melanoleuca

Felis silvestris

Hydromys chrysogaster

Mallomys rotschildi

Patch complexity

0
100
200
300

0
100
200
300

37 patches

257 patches

122 patches

241 patches

0
100
200
300

0
100
200
300

0
100
200
300

0
100
200
300

0
100
200
300

0
100
200
300

Animal-omnivore

Plant-omnivore

Herbivore

Carnivore

Animal-omnivore

Plant-omnivore

Herbivore

Carnivore

Animal-omnivore

Plant-omnivore

Herbivore

Wild cat

Giant panda

Water rat

Woolly rat

300
200
100
0

300
200
100
0

300
200
100
0

300
200
100
0

300
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300
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300
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100
0
The Evo-Devo Challenge

Team

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