Opportunities for Theory in Biological Physics.

1) Chromosome Control.

2) The Polyglutamine Problem.

3) Transcription Initiation Complex.

4) Ribosomal Proofreading.

5) Focal Adhesion Sites.
**DNA/DNA interaction:**
Aqueous electrostatics beyond mean-field theory. (Oosawa)

**DNA/nucleosome interaction:**
electrostatic attraction versus bending stiffness. (Manning)

**Micromechanics (M. Wang)**

Nucleus: 23 chromosomes (1m DNA in micron-sized nucleus)

Gene regulation by compaction.
“Chromosome painting”: 3D-FISH

Statics:
3-D Reconstruction of Nucleus.

DNA-DNA mean spacing: 30-40 Angstrom.
Close-packing is close
Expanded Chromosome Loop (active genes)

Condensed inactive genes

Decondensed, active genes

Inter-chromatin Compartment

Active gene: on surface.

Late replicating gene

Nature Reviews | Genetics

Nucleus is fully accessible to protein transport.
3-D Fish: Chromosome Dynamics (20 minute intervals)
Chromosomal “Diffusion”

Chromosomal Volume and Surface Area vs time.

Hela nucleus A individual

nucleus B

MSD [μm²]

terr 1
terr 3
Fit terr 1
Fit terr 3

volume [μm²]

volume 1
volume 2

surface area [μm²]
surface 1
surface 2

time [min]

20 60 100 140 180 220 260

20 60 100 140 180 220 260
Statics:
How is the “open” architecture of the nucleus maintained and controlled under the osmotic pressure of de-condensed, active DNA sections. Equation of State of DNA bundles is known.

Dynamics:
Chromosome dynamics driven by DNA condensation/de-condensation events triggered by local gene expression:”gene noise”.

*Can we deduce temporal and spatial correlation functions for gene noise from the motion of the chromosomes by fluctuation analysis and relate it to gene activity?

*Chromosome “micro-rheology”?
The Polyglutamine Problem

*Nine* neuro-degenerative diseases are associated with \((CAG)_N\) triplet repeats: Huntingdon’s, spinal dystrophy, ataxia .... CAG is the code for the amino-acid *glutamine*.

C. *Elegans* worm
GFP \((CAG)_N\)

N=82:
Toxic Aggregates
Impaired motility
Proteosome action inhibited.

Aggregates: \(N > 35-40\)

N=19
Homogeneous

N=82 (x 40)
In vitro polyglutamine homopolymer aggregation (N=37)
Aggregation Kinetics (Wetzel):

“Zipper”: Anti-parallel beta sheets.

Not specific for glutamine
“Polymers physics” of alpha-helix forming homopolymers is well understood (Bruno Zimm). Ising model.

Beta-sheet homopolymers: first-order phase transition (Finkelstein)
sheet nuclei: can “infect” unstructured peptide sequences.

Boltzmann Distribution!
but…..

Huntingtin exon 1 actually produces a PolyQ/PolyP block copolymer!
Many proteins can be made to misfold into beta-sheet
Gõ model.

\[ i = 1, 2, \ldots, N \]

\[ M_{i,j} \quad (\text{non specific}) \]

\[
\begin{bmatrix}
0 & 1 & 0 \\
0 & 0 & 1 \\
1 & 0 & 1 \\
0 & 1 & 1
\end{bmatrix}
\]

*Monte-Carlo.
- Beta-sheet: off-diagonal entries.
- Competing energy minimum versus folding pathway
1) Eukaryotic Transcription Complex: “Structural Calculator”

Silencers/enhancers modulate gene expression.
RNA Polymerase
TATA box binding protein
Transcription Factor
Nucleosomes
Basal Complex
RNA Polymerase
Universal Molecular Computer
“Boolean logic” (T.Hwa)
Complex controls statistically the rate of gene expression by altering the RNA Polymerase binding energy.

*How do large protein complexes “grow” and form well-defined, unique structures?

*How is the “signal” communicated from silencer/enhancer to the RNA Pol binding site? (super-allostery?)

*Is the DNA bending stress relevant? (Austin)
Thermal fluctuations play a key role:

Basal Complex

TATA box binding protein: 
*near-symmetric dimer*

Electron Micrograph (TFIIA, TFIIB)
TATA box:
Thermal sliding fluctuations.
Thermal orientational fluctuations.

Disaster ?? No, apparently
F of order few kT

Positional and orientational order:
improve when TFIIA&B are added.
Statistical building scheme?

Crystal Structure of:
TFIIA, TFIIB, TBP
complex known.
Ribosomes.

Ribosome must match right Amino Acid (20) to given RNA codon.
Ribosome crystal structure (2.4 Angstrom):
Thermodynamic error rate for insertion of wrong amino-acids is much too high!

\[ P(\text{wrong}) \exp\left( \frac{F_{\text{right/wrong}}}{kT} \right) \]
Attach fluorescent donors and acceptors to amino acids, ribosome. (S.Chu)
Donor: Amino-Acid #1

Acceptor: Amino-Acid #2

Time record:

Finds two “proofreading” check-points.
Hopfield proofreading:

Excited transition state.

Ribosome

Fresh Amino Acid (right or wrong)

Amino Acid Incorporated (mostly right)

Eject amino acid (mostly wrong)
Focal Adhesion Sites: Motor protein regulation
Rigidity Sensing

QuickTime™ and a Video decompressor are needed to see this picture.
• Soft substrate: slipping motion, tension in the pN range.
• Rigid substrate: stationary, tension in the nN range.
• External tension stimulates reinforcement.
• **Integrin proteins** linked to Actin filaments by Adaptor proteins.
(Sheetz)
Mechanical Activation?

Lever arm L: (30 nm)

Traction F:

Mechanical Work:
\[ W = F L \sin \theta G \]
\[ 10 k_B T \]
Mechanical Activation Integrin.

Tyrosine Phosphatase Activation. (RPTP )

Src kinase pathway.

Adhesion-site Reinforcement.
Linear Elasticity

External surface stress:

\[ \frac{M_y}{l_k} \frac{r}{r} \]

\[ G_{ijkl} \frac{r}{r} \frac{r}{r'} \frac{M_y}{l_k} \frac{r}{r'} d^2 r' \]

- Does not depend on Young’s Modulus!
- “Dynamic” sensing?
Integrin-Ligand Rupture

(K. Kinoshita & E. Evans, 2003)

$$\langle F_{RUP} \rangle \sim f \ln \frac{k_{off} f}{k_B T} \exp \frac{U}{k_B T}$$

Loading Rate

15 pN

$$k_{off} \exp \frac{U}{k_B T}$$

Activation Energy

2000/sec