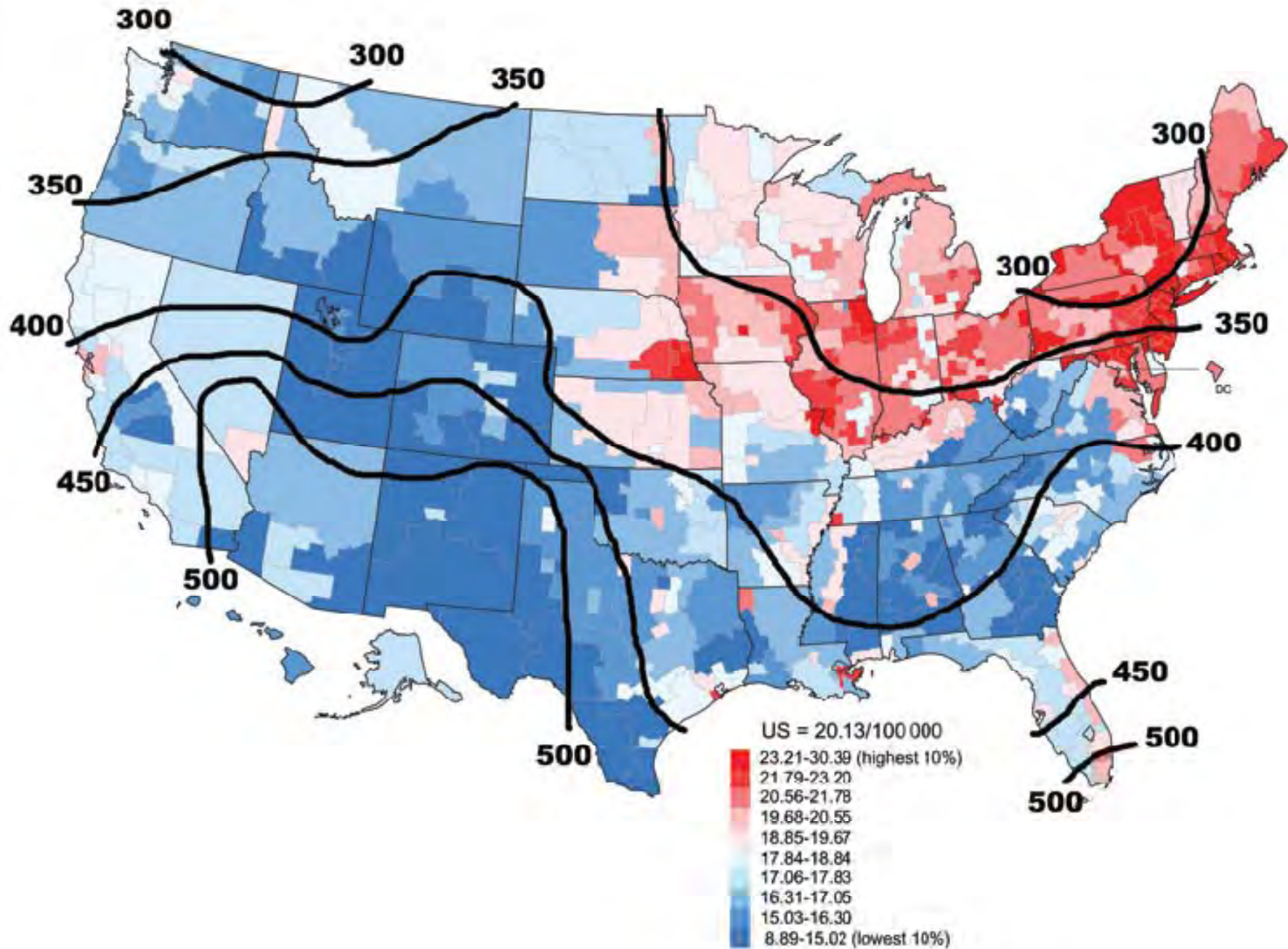
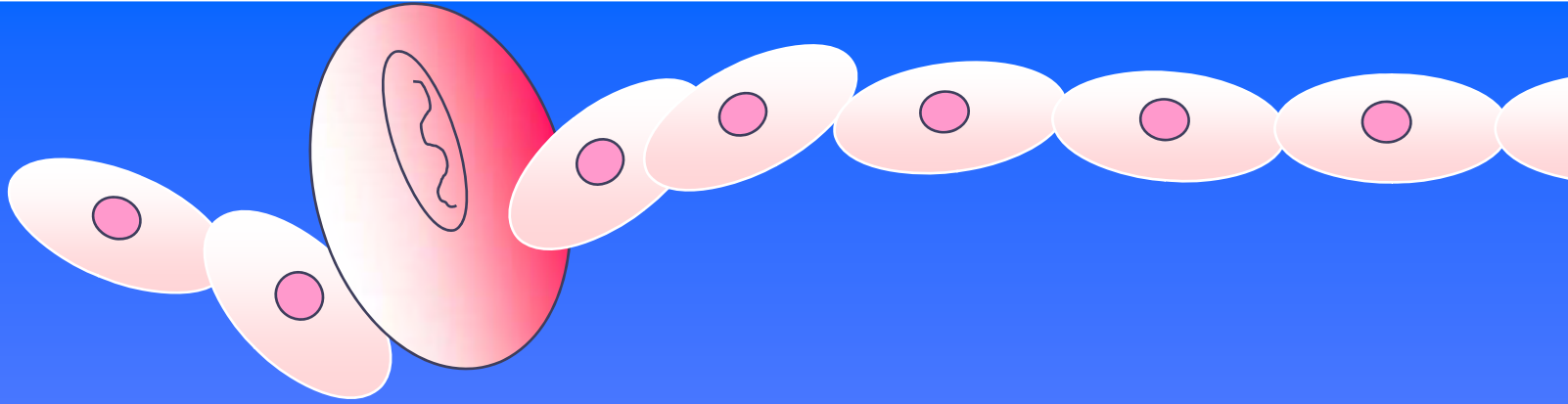


**How it works  
UCSD-TV  
April 8, 2009**

**Cedric F. Garland, Dr.P.H., F.A.C.E.**  
Professor, Department of Family and Preventive Medicine  
School of Medicine

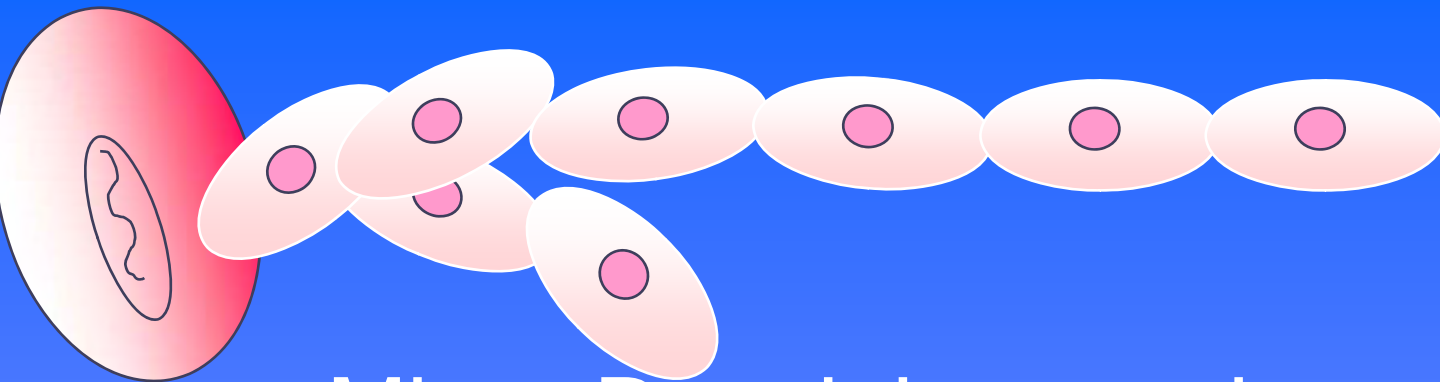
**April 8, 2009 12:00 Noon**





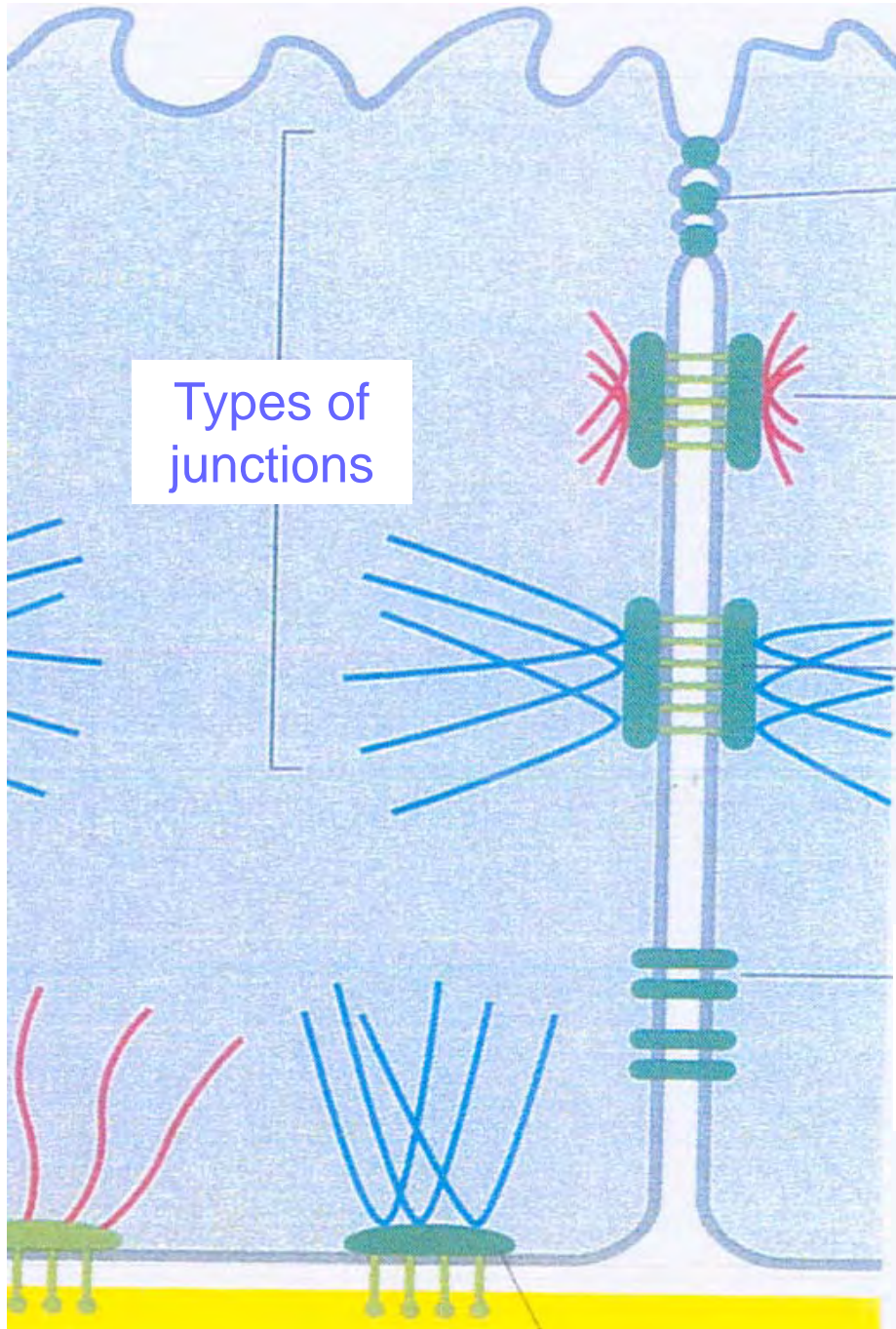
## Classical theories of carcinogenesis

- Mutation theory: Boveri, 1902
- Two-hit theory: Knudson, 1980.
- “Many-hit” theory: A number of hits are needed (authors include Vogelstein et al., 1991).



## Micro-Darwinian carcinogenesis and Vitamin D deficiency induced D-volution

- In vitamin D deficiency, the first lesion is harm to the intercellular junction.
- This unleashes natural selection.
- Natural selection is the engine of growth of the cancer.



Types of junctions

Tight junctions seal gaps between epithelial cells

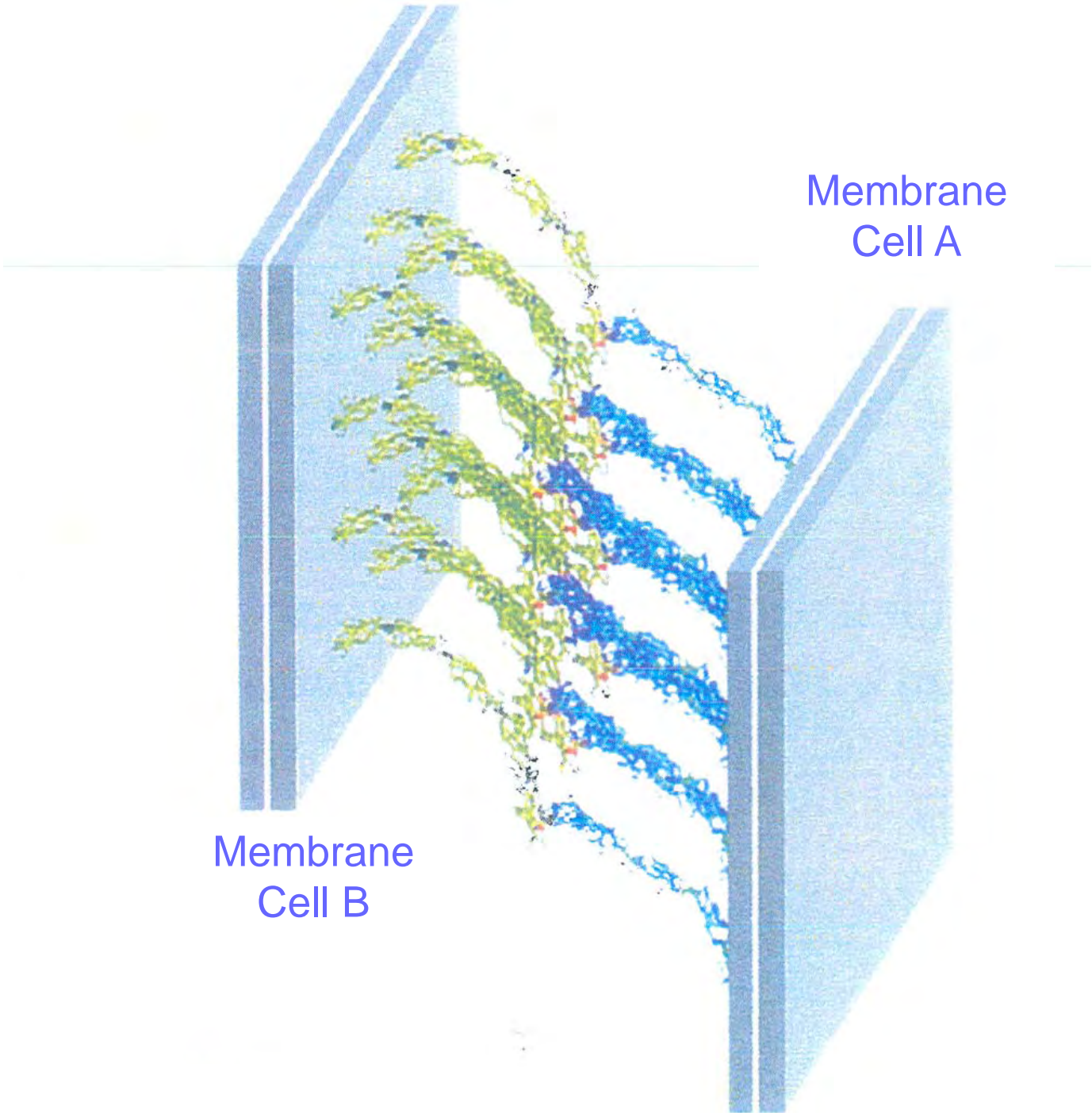
Adherens junctions connect actin filament bundles between cells

Desmosomes connect intermediate filaments in adjacent cells

Gap junctions allow passage of small water-soluble molecules between cells

Membrane  
Cell A

Membrane  
Cell B



Classical cadherin  
(E-cadherin)

Fat-like cadherin

Seven-pass  
transmembrane  
(flamingo) cadherin

Protein kinase  
cadherins

Desmosomal cadherins

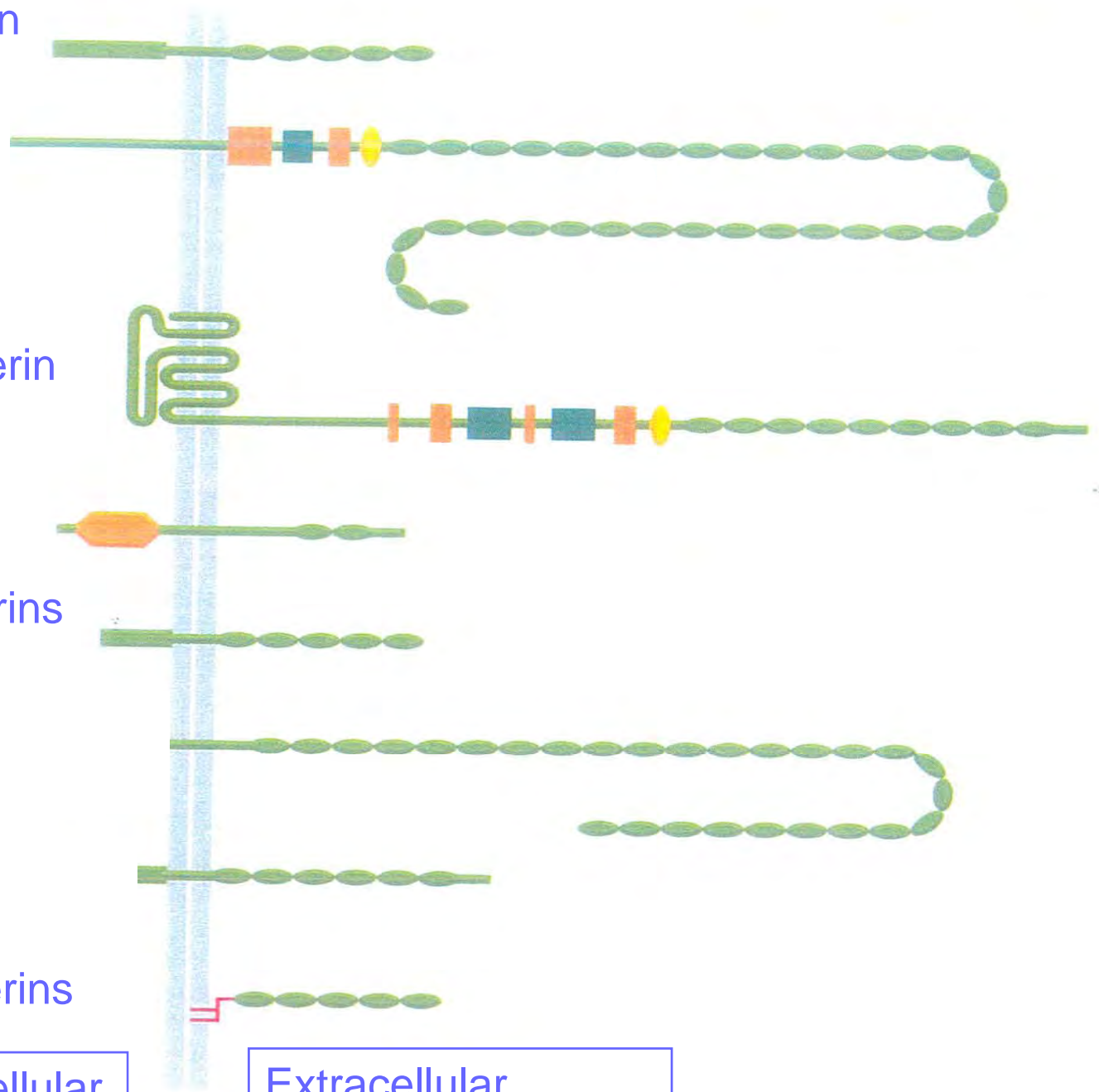
Cadherin 23

Protocadherins

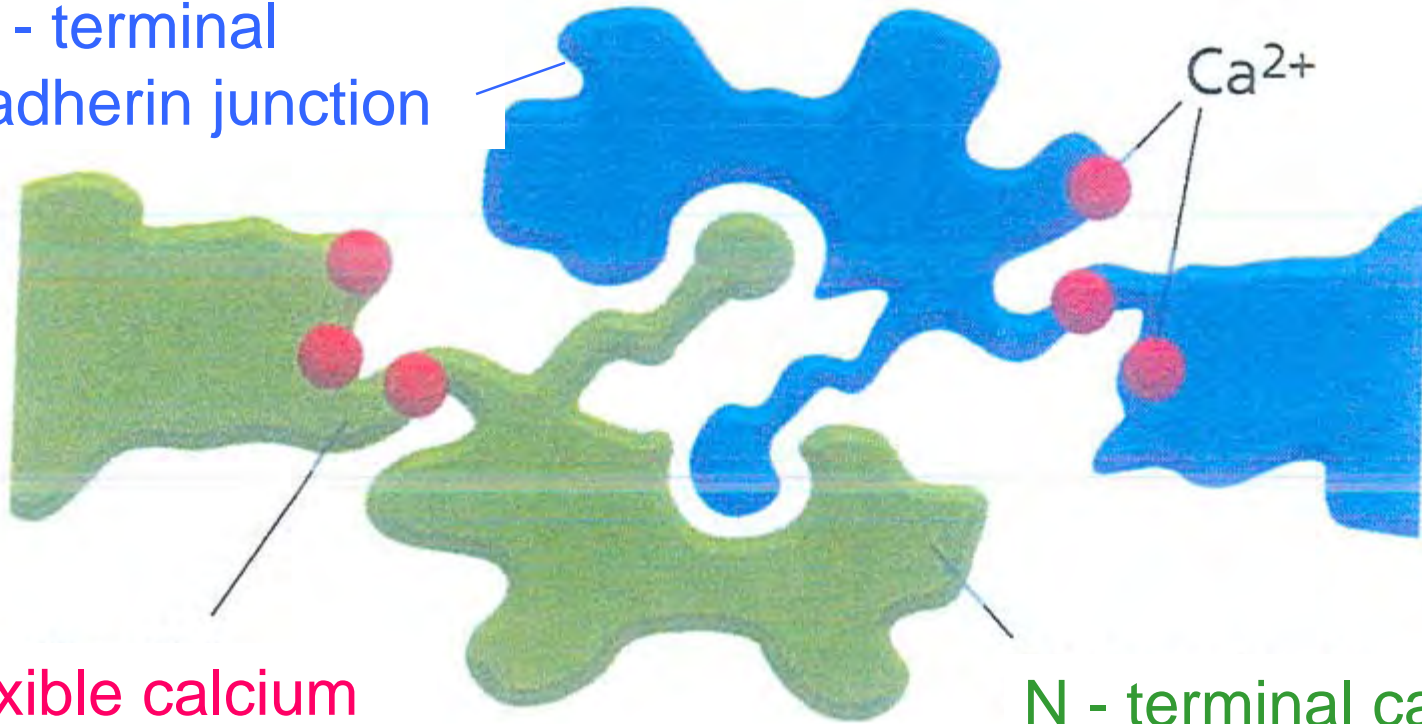
T cadherins

Intracellular

Extracellular



N - terminal  
cadherin junction



Flexible calcium  
dependent hinges

N - terminal cadherin  
junction

Coupling between cadherins from two cells

Gene-fold changes in a colon cancer cell line (SW480-ADH)  
after 48 hours exposure to 1,25 (OH)<sub>2</sub> vitamin D<sub>3</sub>

Cytoskeleton/adhesion

+ 39	Type II keratin (hHKb1)
+ 14	Gravin
+ 12	E-cadherin
+ 7	Keratin 15
- 4	Calgizzarin

GTPases and related

+ 42	RAB2
+ 21	RA1BP1-interacting protein
+ 4	Breast cancer anti-estrogen resistance protein (BCAR3)

Channels and transporters

+30	Putative monocarboxylate transporter (MCT)
+15	3- <i>beta</i> -hydroxysteroid dehydrogenase (3- <i>beta</i> -HSD)

Apoptosis related

+24	Insulin-like growth factor binding protein-3 (IGFBP-3)
+11	DAP-1 <i>alpha</i>
+10	TNF- <i>alpha</i> converting enzyme
+7	gadd45
+6	Ceramide glucosyltransferase
+6	Prostate apoptosis response protein (par-4 )
-5	CD27BP (Siva)
+74	17- <i>beta</i> - hydroxysteroid dehydrogenase (17-HSD)
+20	Cytochrome P450 III A

DNA cell cycle

+ 24	G <sub>0</sub> S2
- 4	Cyclin F

# DINOMIT Theory of Cancer

**D**isjunction

**I**nitiation (genetic variation)

**N**atural selection

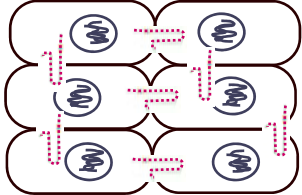
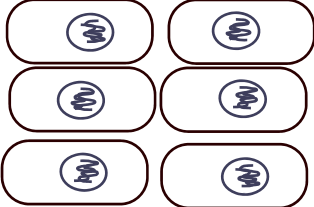
**O**vergrowth

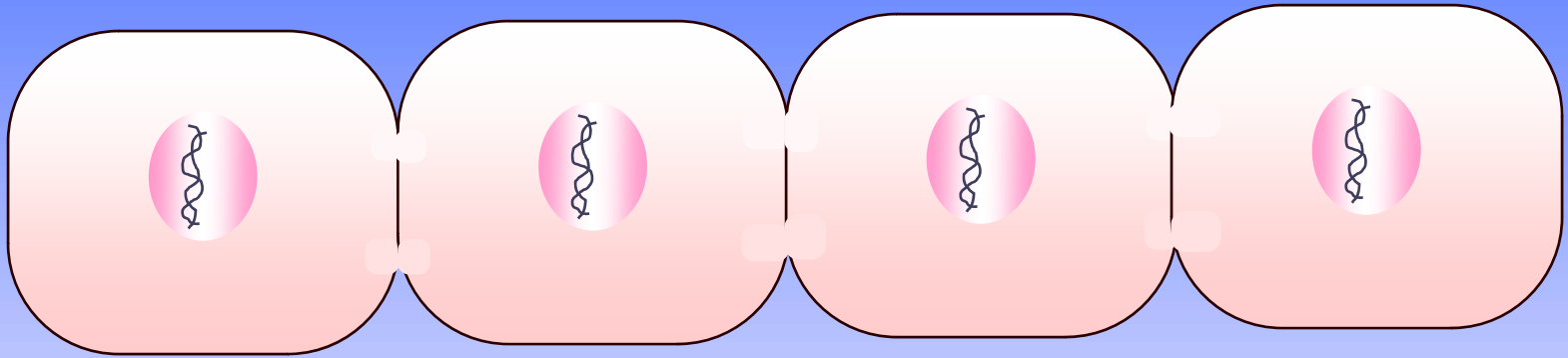
**M**etastasis (spread)

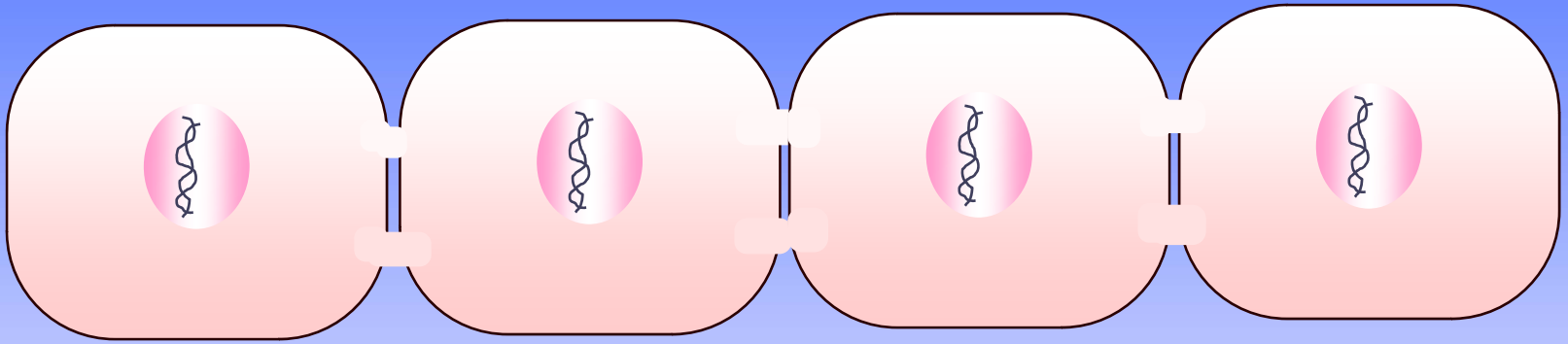
**I**nvolution (cancer stops or slows)

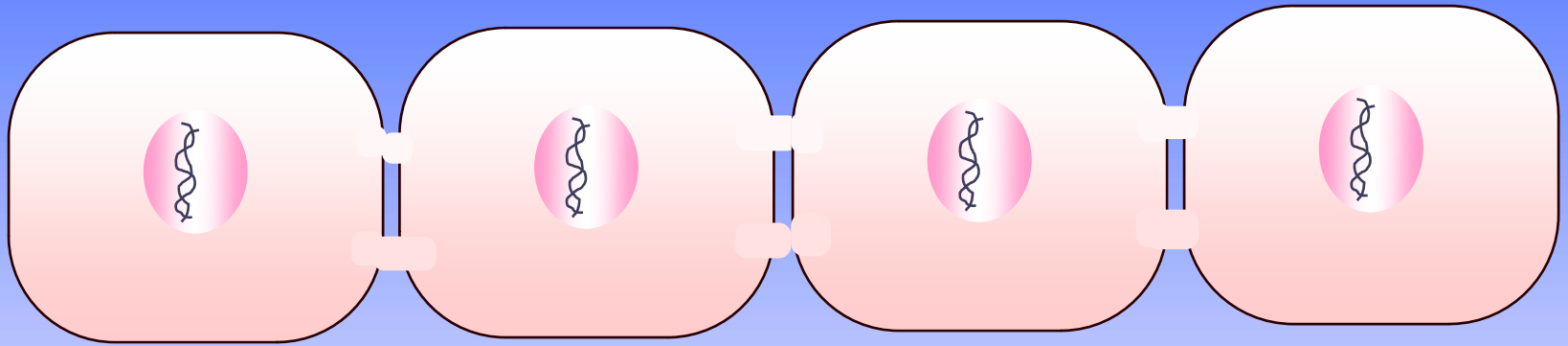
**T**ransition (becomes chronic condition)

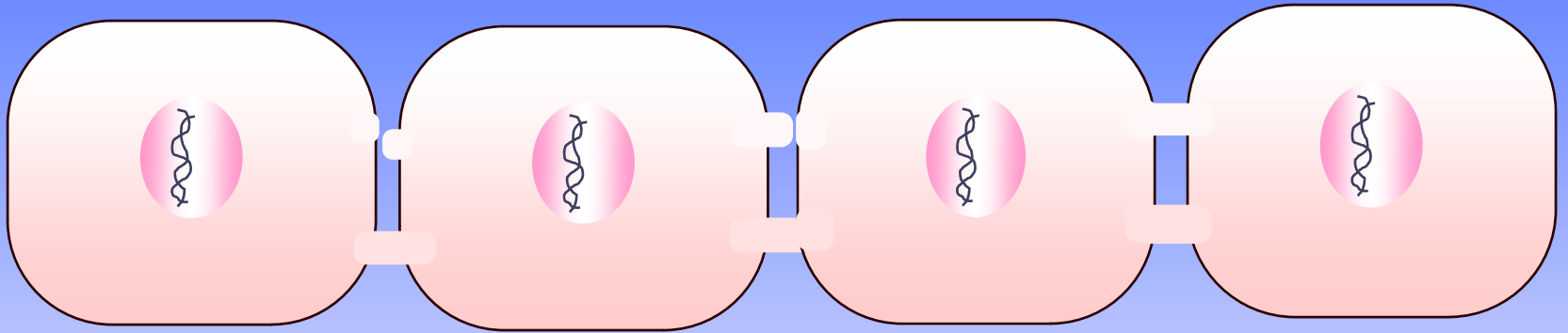
# DINOMIT Earliest Phase - Disjunction

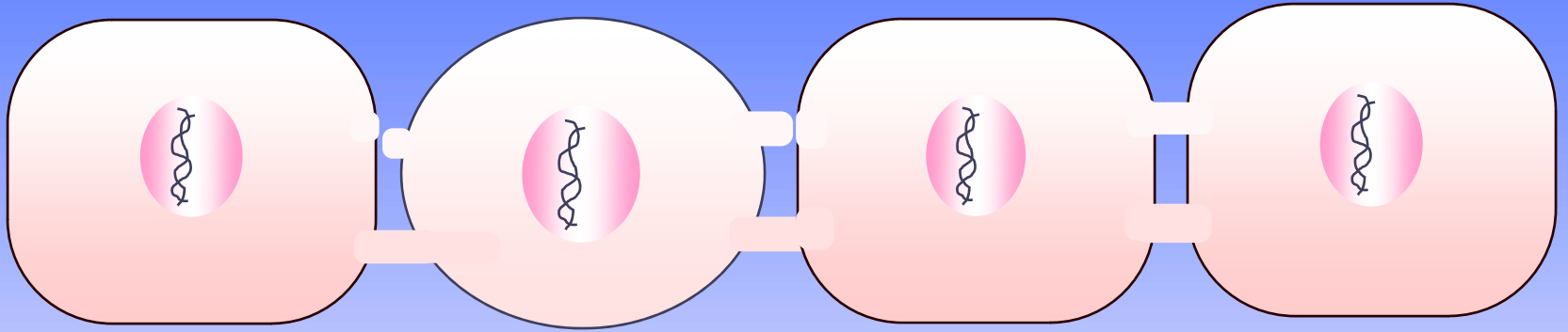
<u>Phase</u>	<u>Diagram</u>	<u>Process</u>	<u>Preventive or therapeutic action</u>
Vitamin D Replete (Normal)	 A diagram showing a 3x2 grid of six rounded rectangular cells. Each cell contains a nucleus with a nucleolus. Red dashed lines with arrowheads connect the cells at their corners, representing tight junctions. Additional red dashed lines with arrowheads connect the cells horizontally and vertically, representing intercellular communication.	Tight junctions intact Intercellular communication, growth inhibition and cell cycle normal non-mitotic	Maintain 25(OH) D level of 40- 60 ng/ml
Disjunction Due to Vitamin D Insufficiency	 A diagram showing a 3x2 grid of six rounded rectangular cells. Each cell contains a nucleus with a nucleolus. The cells are slightly separated from each other, indicating disjunction. There are no red dashed lines between the cells, representing the loss of tight junctions and intercellular communication.	Tight junctions weak or absent. Cells separate from each other very slightly. Cadherins lost or weak. Contact inhibition lost. Beta-catenins relocate. Natural selection begins.	Upregulation of tight junctions and cadherins by vitamin D metabolites

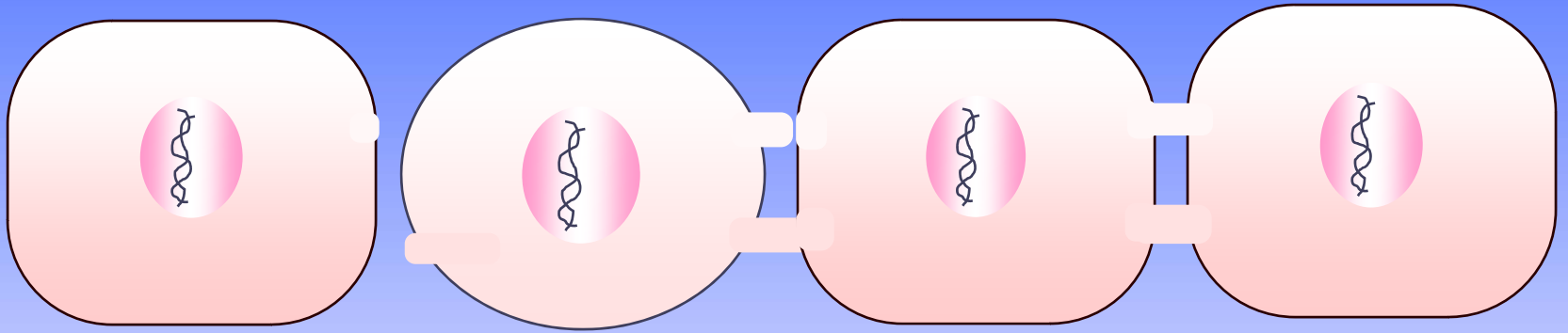


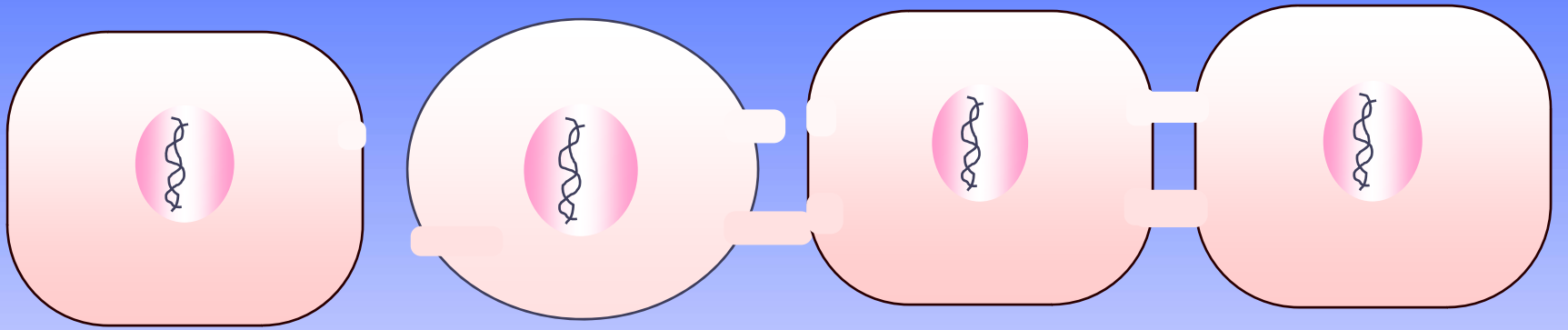


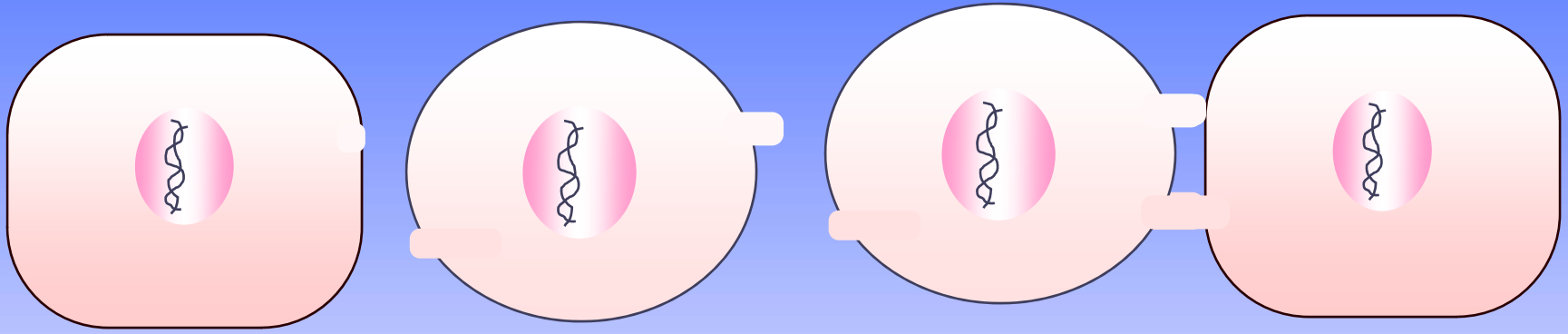


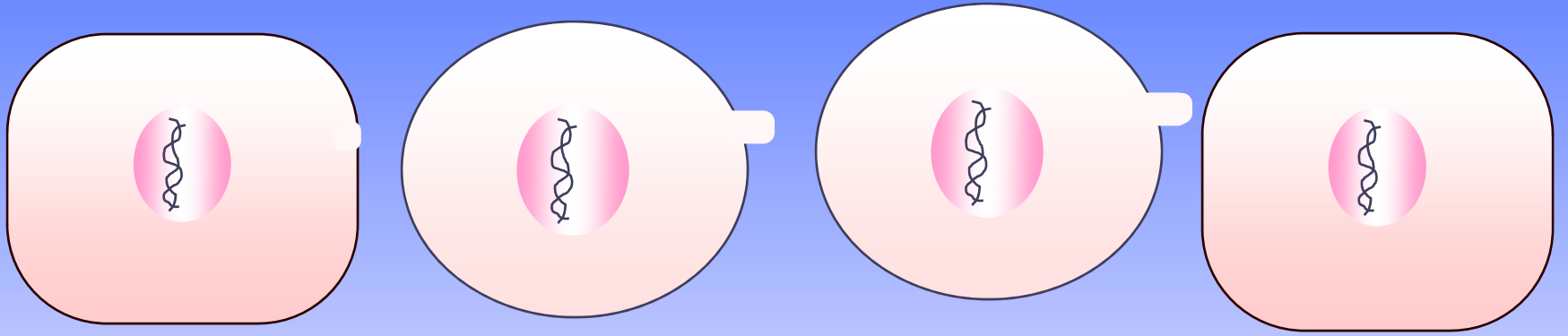


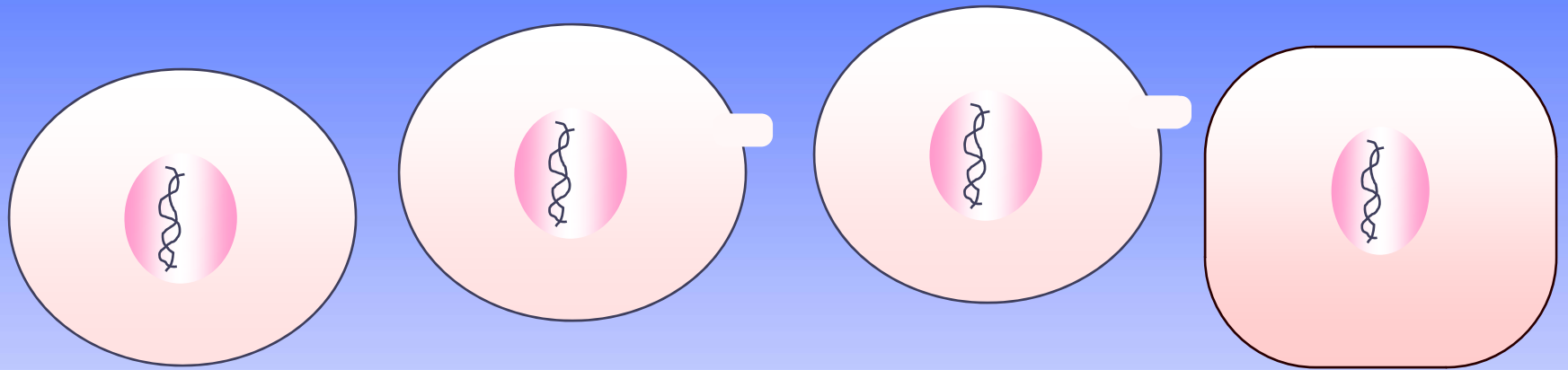


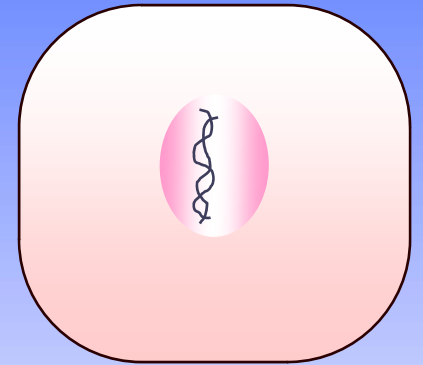
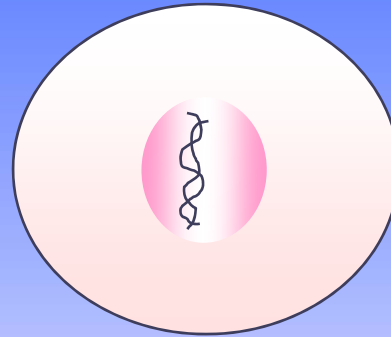
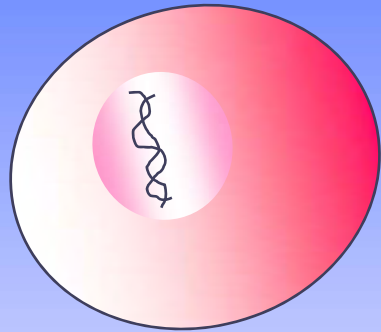
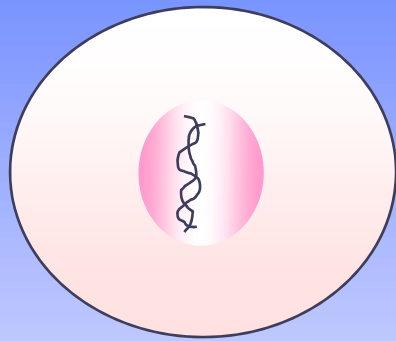


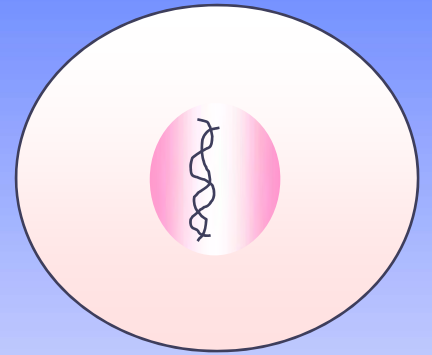
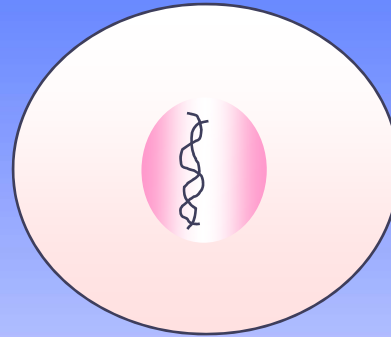
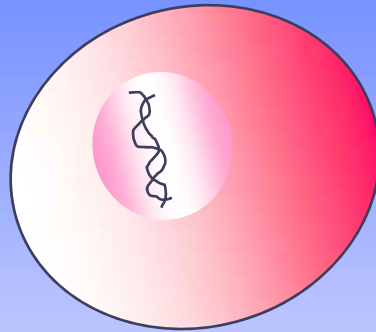
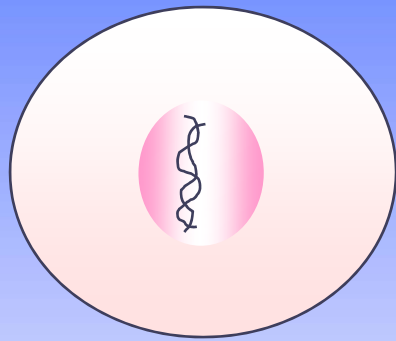


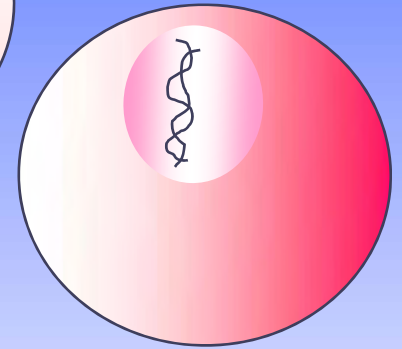
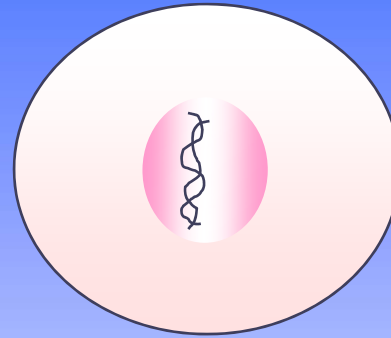
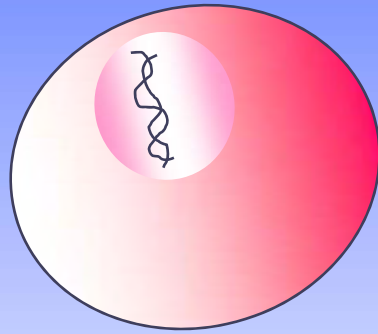
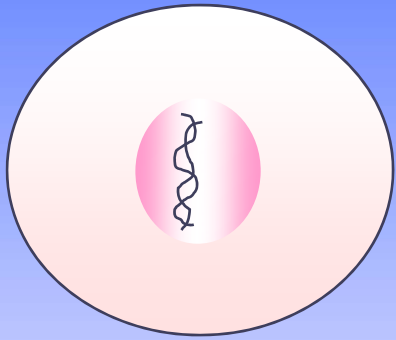


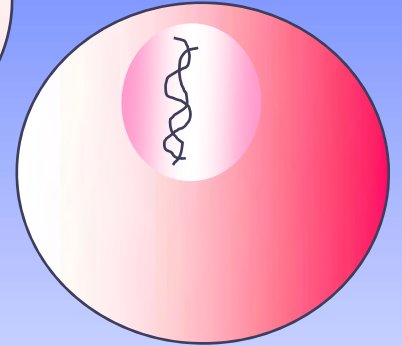
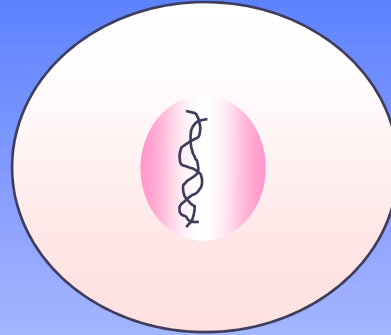
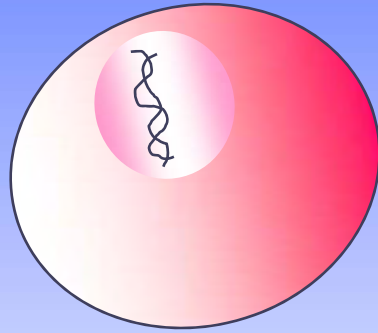
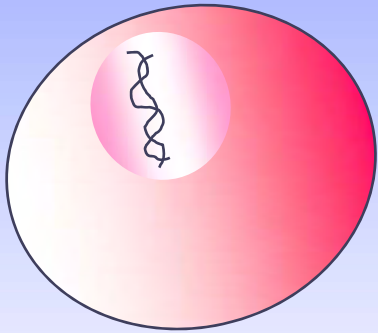


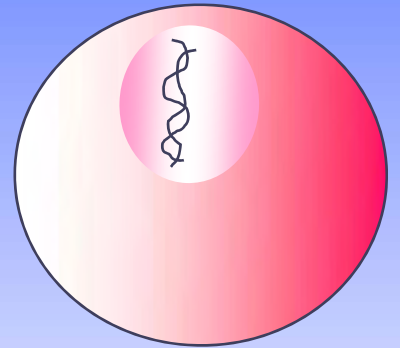
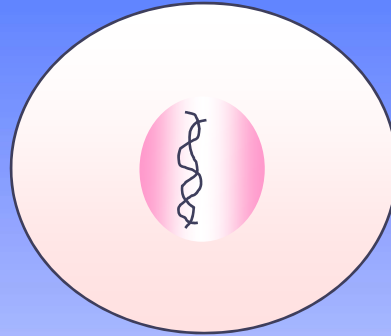
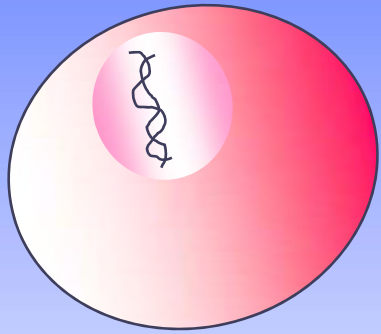
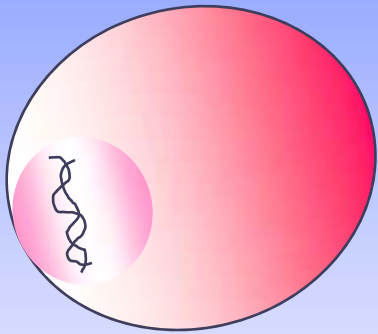


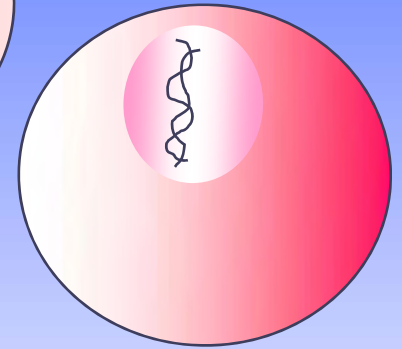
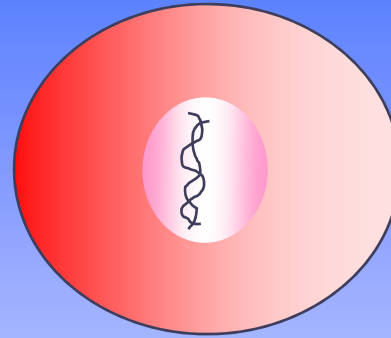
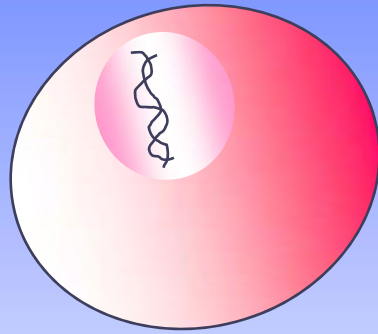
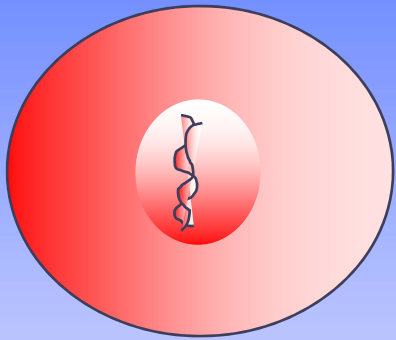


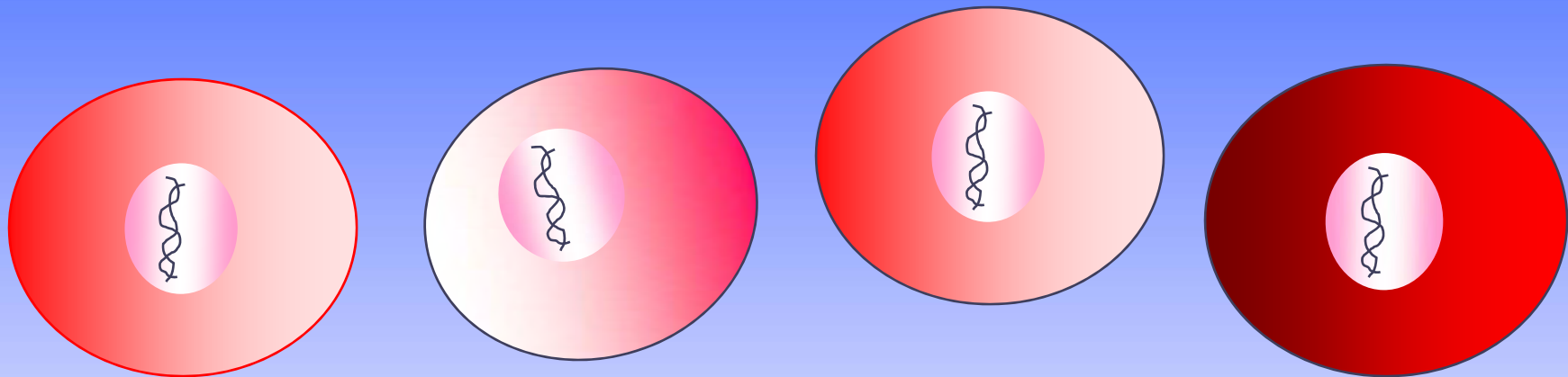


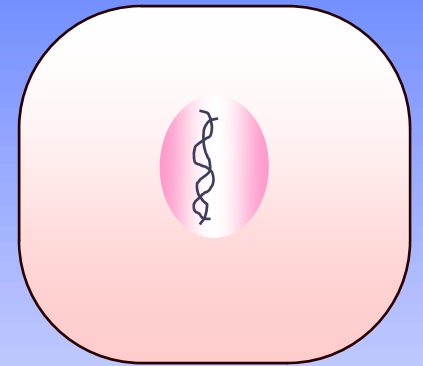
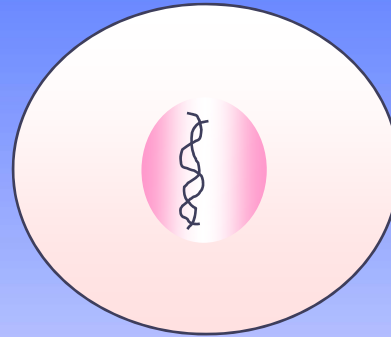
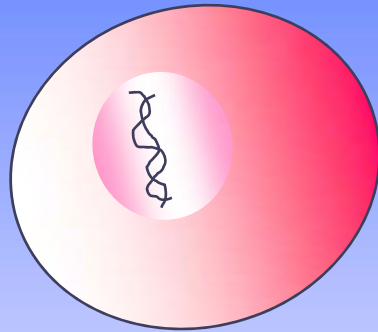
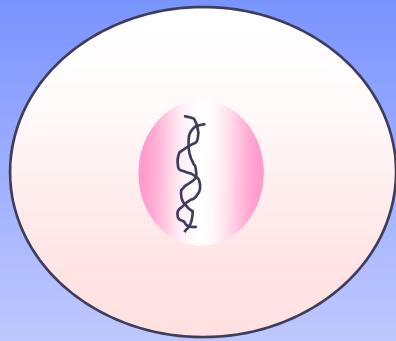


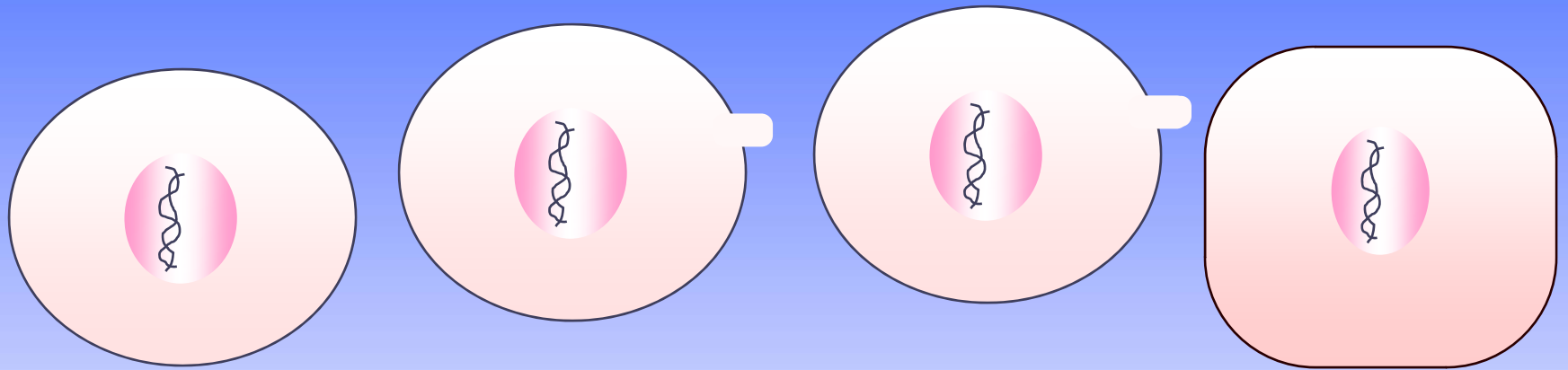


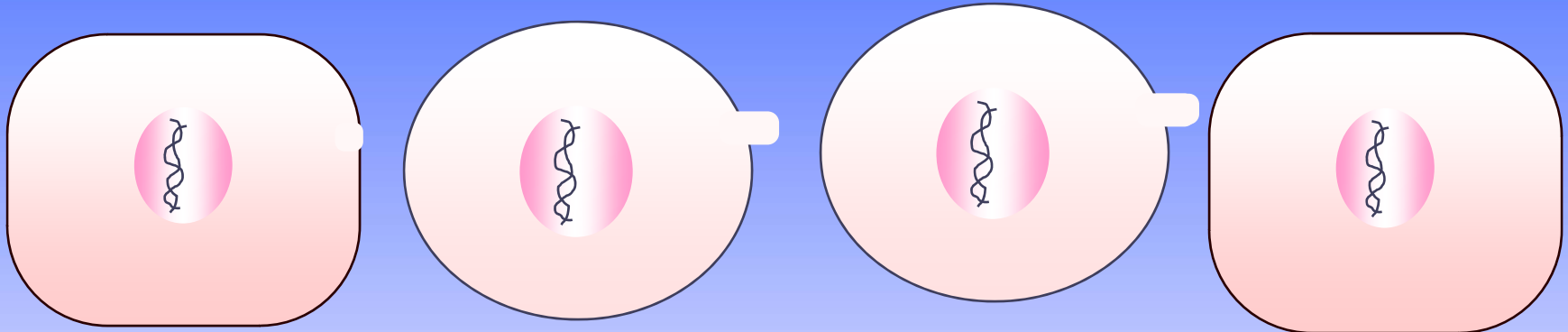


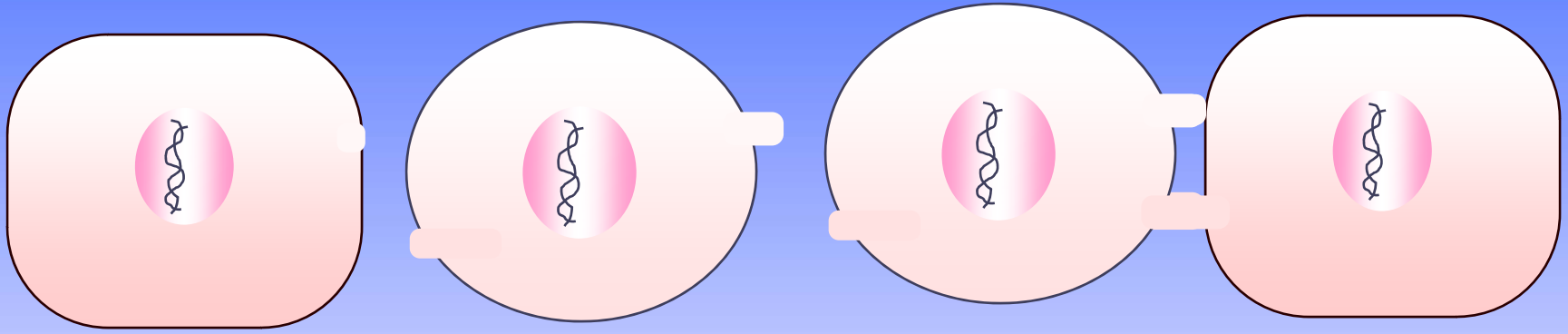


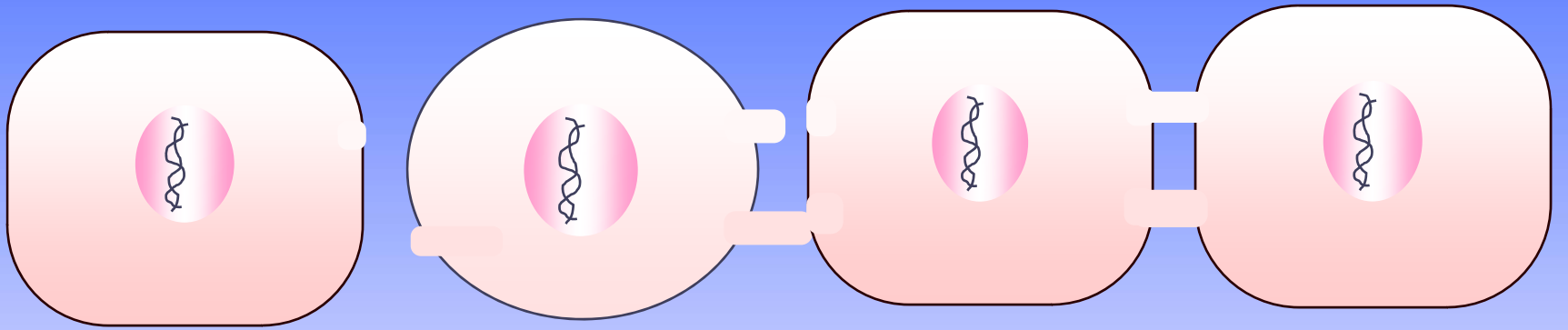


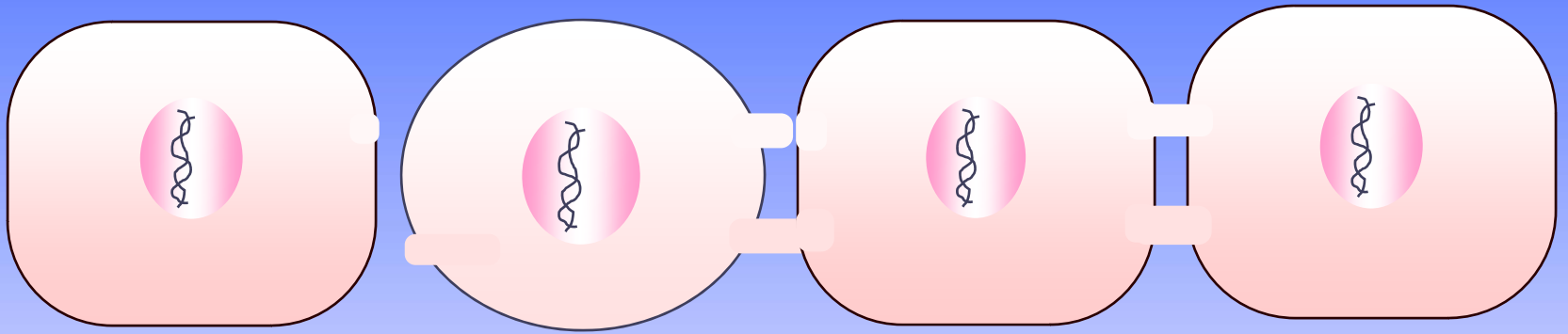


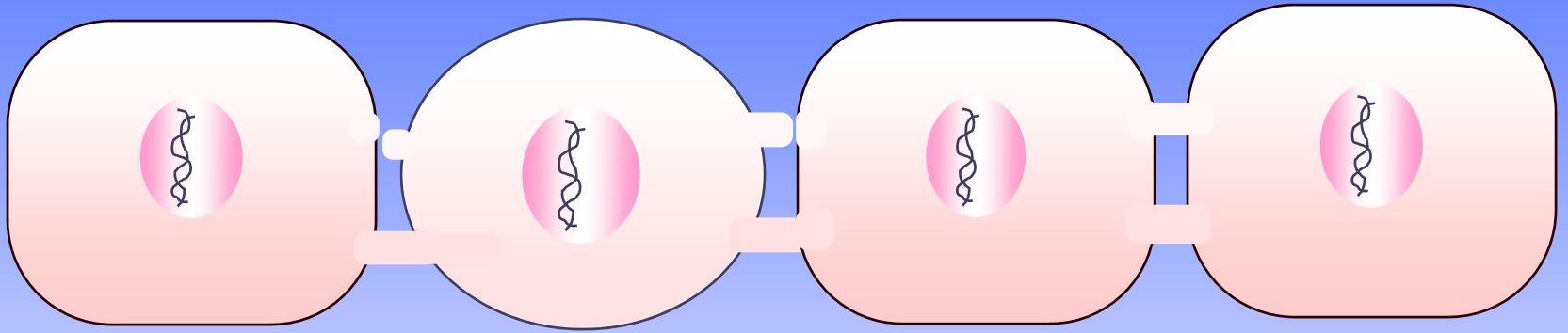


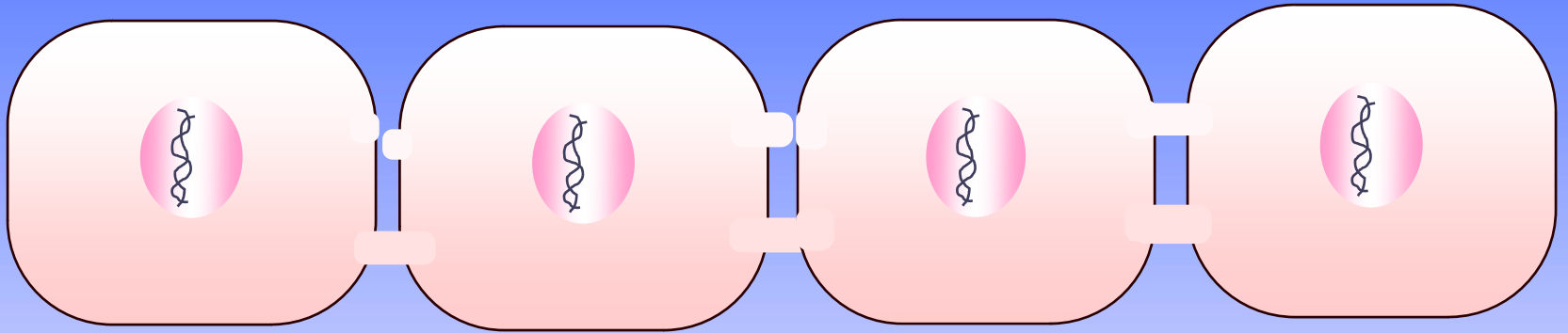


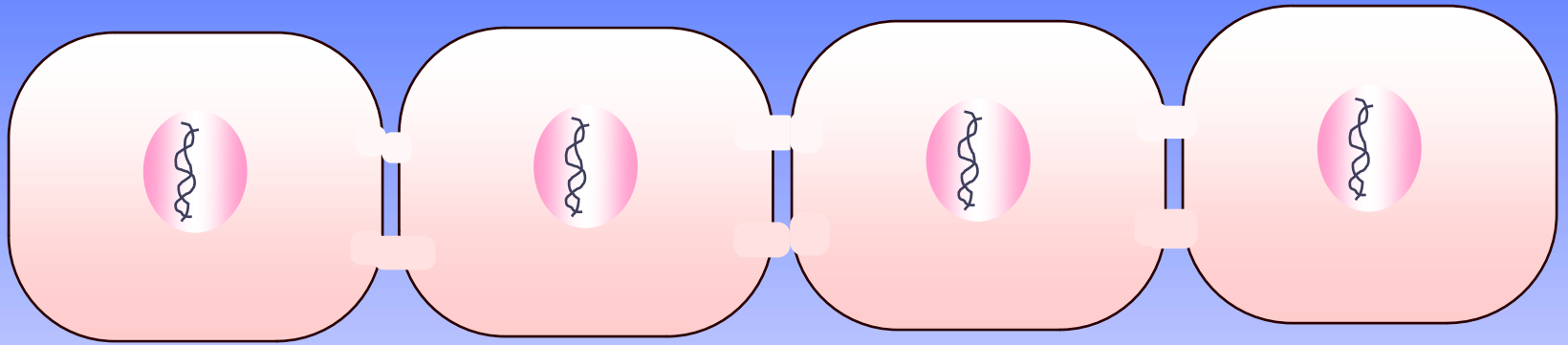


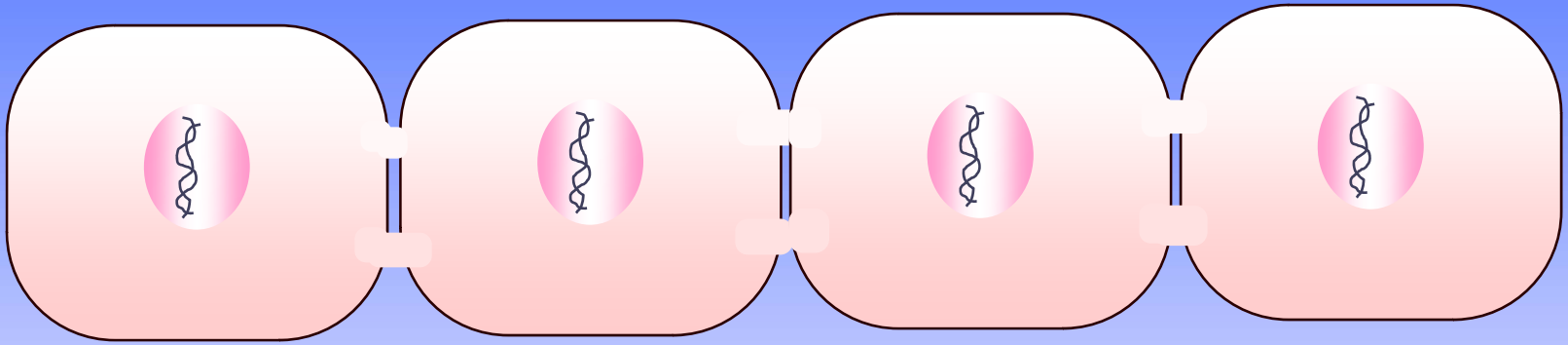


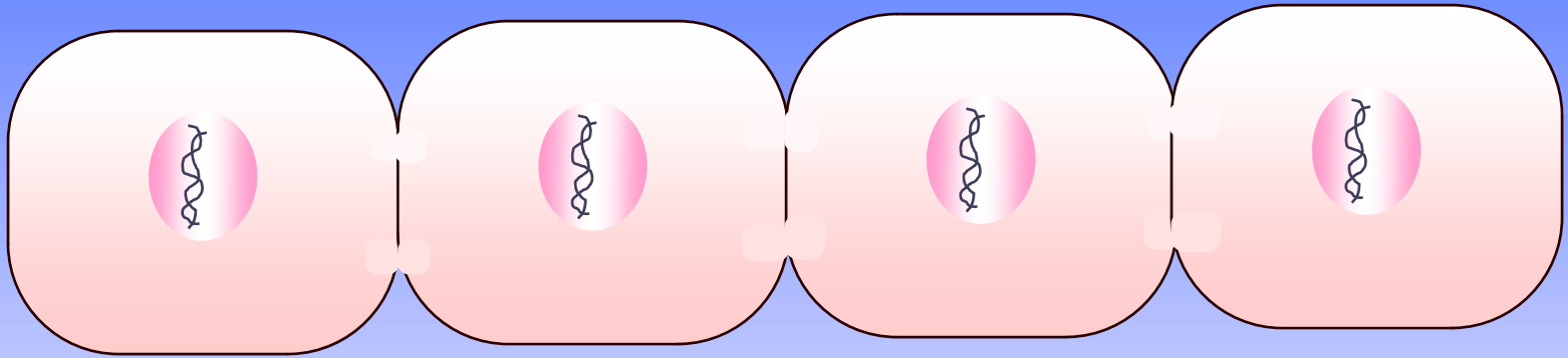




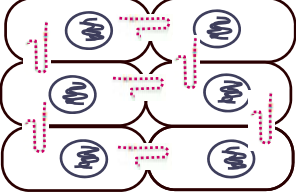
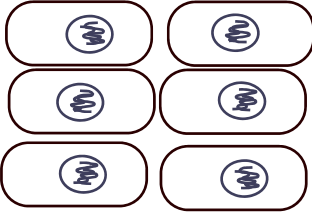

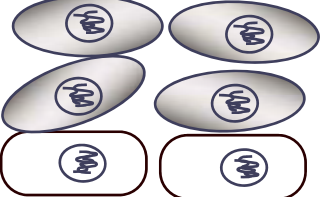
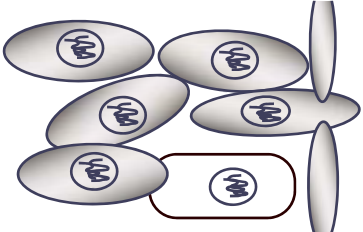




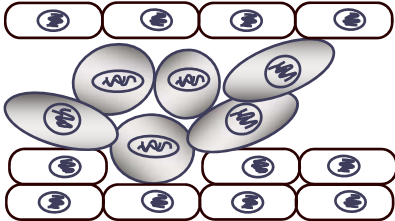
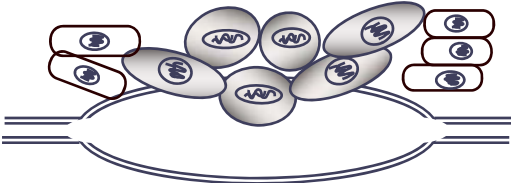

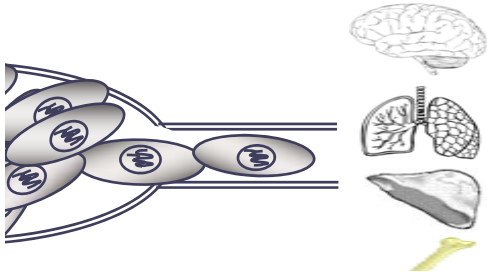
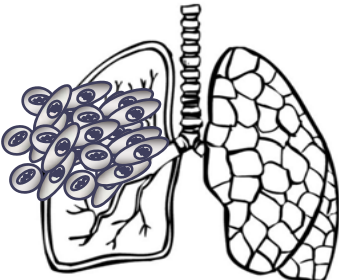




# DINOMIT Phases

<u>Phase</u>	<u>Diagram</u>	<u>Process</u>	<u>Preventive or therapeutic Action</u>
Vitamin D Replete (Normal)		Tight junctions intact Intercellular communication, growth inhibition and cell cycle normal non-mitotic	Maintain 25(OH) D level of 40- 60 ng/ml
Vitamin D Insufficiency Disjunction		<b>(D)</b> Tight junctions weak or absent. Cells separate from each other very slightly. Cadherins lost or weak. Contact inhibition lost. Beta-catenins relocate.	Upregulation of tight junctions and cadherins by vitamin D metabolites
Initiation and Natural Selection		<b>(I)</b> Initiation or variation begins.. <b>(N)</b> Natural selection favors reproduction of rapidly mitotic, aggressive cells. These appear as new stem cells (Wicha et al., 2008)	Vitamin D maintains tight junctions, contact inhibition, and normal growth and cell cycle
Overgrowth - Clonal Expansion		<b>(O)</b> Overgrowth of rapidly mitotic, aggressive progeny predominate, a 1% advantage will fill compartment in 9000 generations	Vitamin D favors apoptosis and normal cell cycle
Lysis and Penetration of Basement Membrane		Overgrowth continues with a few cells penetrate basement membrane while consuming essential amino acids making up membrane	Vitamin D inhibits lysis of basement membrane, Promotes sharing of micronutrients; Maintains intercellular junctions and desmosomes

# DINOMIT Phases

<u>Phase</u>	<u>Diagram</u>	<u>Description</u>	<u>Prevention or Therapeutic Action</u>
Stromal Phase		Overgrowth extends into underlying tissue	Re-establish tight junctions between cancer cells
Lymphatic Entry Phase		Overgrowth continues into lymphatic circulation	Re-establish tight junctions Prevent lymphatic entry
Lymphatic Growth Phase		Overgrowth colonizes Lymph nodes	Re-establish tight junctions Confine malignancy to lymph nodes
Lymphatic Transport Phase		Lymphatics transport cells to brain, lung, liver, bone	None
Metastasis (colonization) Phase		<b>(M) Malignant cells colonize remote host site</b>	If VDR still present, re-establish tight junctions, downregulate VEGF, reduce growth rate, restore contact inhibition

## DINOMIT Concluding Phases

**(I) Involution** - Malignant cells may move into a phase of slowed or arrested growth, or involution. They retain the potential for growing if the vitamin D level drops. Involution is most likely to occur in summer and early fall. Surveillance continues. Requires no less than 40-60 ng/ml 25(OH)D.

**(T) Transition – Conversion to chronic condition.** – Malignancy becomes a background concern as long as vitamin D status is maintained. If adequate vitamin D status is not maintained, the malignancy grows further and can cause death. Many cancers can be transitioned to chronic conditions. Surveillance continues. Requires no less than 40-60 ng/ml 25(OH)D.

# DINOMIT Theory of Cancer

**D**isjunction

**I**nitiation (genetic variation)

**N**atural selection

**O**vergrowth

**M**etastasis (spread)

**I**nvolution (cancer stops or slows)

**T**ransition (becomes chronic condition)

## How much vitamin D should I take?

- It depends on your 25-hydroxyvitamin D serum level.
- Enough to get the serum level to 40-60 ng/ml (100-150 nmol/L)
- There's an increase of approximately 7-10 ng/ml with each 1000 IU.
  - Example: If you want to raise your serum by 20 ng/ml, you could try taking 2000 IU/day.

# Should Cancer Patients Take Vitamin D?

- YES!
- Test for serum hydroxyvitamin D
  - Get to 40-60 ng/ml (100-150 nmol/L)
  - Test for ionized calcium
- Based on what we know about intercellular junctions, vitamin D can help restore the natural links and slow or prevent cancer growth.

# How do I get vitamin D?

- From the sun, our body's original source
  - Don't burn
  - Amount depends on latitude, skin color, body weight, time of year but, in general about
    - 10-15 minutes/day
      - Between the hours of 11 am-1 pm
      - 40% of body exposed

# How do I get vitamin D? (cont.)

- Food—*not* a natural source of vitamin D for most people. (you'd need about 5 quarts of milk/day or 5 servings of oily fish/day).
- Supplements: D3-cholecalciferol. Take whatever is necessary to get serum levels to 40-60 ng/ml (100-150 nmol/L)

# Known contraindications

Vitamin A	Uses same receptors >6000 IU/day too much ?1000 IU/day enough
Granulomatous diseases, TB, Sarcoidosis	Run high 1,25(OH)D, may become hypercalcemic

# Should I be tested for vitamin D?

- Absolutely! Establish a baseline
- Test until in protective range:
  - 40-60 ng/ml (100-150 nmol/L). It takes about 3 months for the D level to stabilize with a new dose.
  - Then test in March each year (lowest level), then August/September (highest).