

1. History of Bioprocessing

10,000 - 7,000 BC	Wine making develops in Eastern Mediterranean. Dionysus credited with invention.
7,000 - 5,000 BC	Beer develops in Egypt and Babylon.
5,000 BC	Cheese making - some medicinal properties believed
4,000 BC	Yeast used for leavening bread.
500 BC - 0	Vinegar referenced in old testament.
0 - 500 AD	Algae cultivated for food by Aztecs.
?	Yogurt, sauces and fermented meats in orient

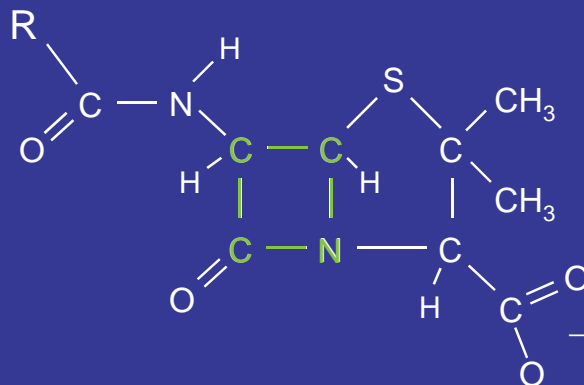
1600	Fermentation used (latin for “yeast” = fermentum), meaning a chemical change accompanied by effervescence.
1680	Van Leeuwenhoek observed yeast cells in fermented beer.
1781	Pressed Baker’s Yeast produced by Dutch Process . Improvement in handling of yeast through mid-1800s.
1798	Jenner demonstrated ability to confer resistance to smallpox by vaccination.
1837	Cagniard-Latour , Schwann and Kutzing independently hypothesized that yeast was a “living thing.” Cell Theory . Notion ridiculed by leading chemists.

- 1847 **Blondeau** (Physics professor) studied fermentations of lactic acid, butyric acid, acetic acid and urea. Hypothesized that different fermentations carried out by different fungi.
- 1856 **Pasteur** demonstrated that living yeast cells ferment sugar into ethanol and carbon dioxide.
Pasteur noted cylindrical organisms produce butyric acid only in absence of oxygen.
- 1859 **Darwin** publishes **The Origin of Species**.
- 1877 **Pasteur** noted relationship between microorganisms and infectious disease.

- 1881 **Koch** developed techniques for the handling and maintenance of pure cultures of organisms. Heralded modern industrial fermentation technology. Commercial production of lactic acid by an anaerobic fermentation.
- 1894 **Takamine** patented process to isolate diastatic enzymes from molds (enzymes which break down starch in malt).
- 1916 -
1918 Germany produces Baker's Yeast grown on molasses as a protein supplement, and produces glycerol by fermentation. Great Britain produces acetone and butanol by an anaerobic process requiring a pure strain. (Last acetone-butanol fermentation in RSA until mid-1980s.)

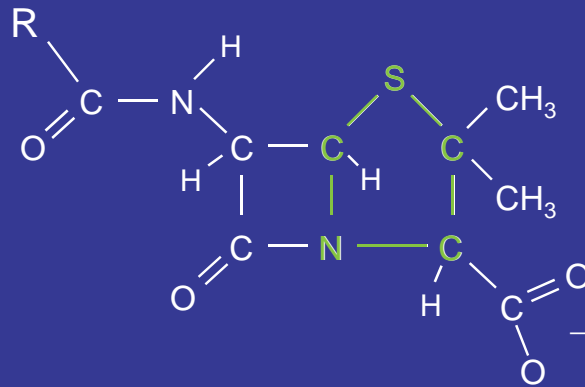
- 1923 Commercial production of citric acid by surface cultures. (In 1989 100% of the world production - 350,000 t - is by submerged fermentation.)
- 1929 **Fleming** demonstrated that a mold contaminant in a petri dish caused bacterial death.
- 1940 **Florey** and **Chain** isolated penicillin, elucidated its structure and demonstrated its bactericidal properties.

Penicillin



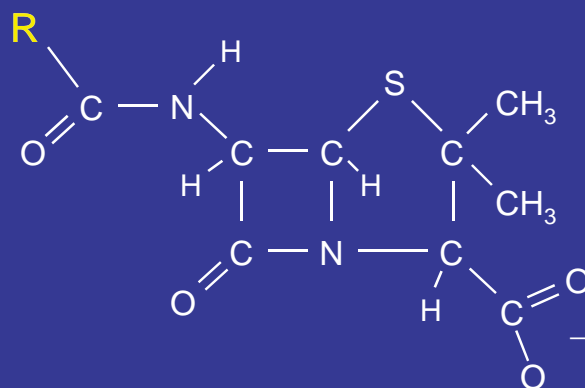
β -Lactam Ring

Penicillin



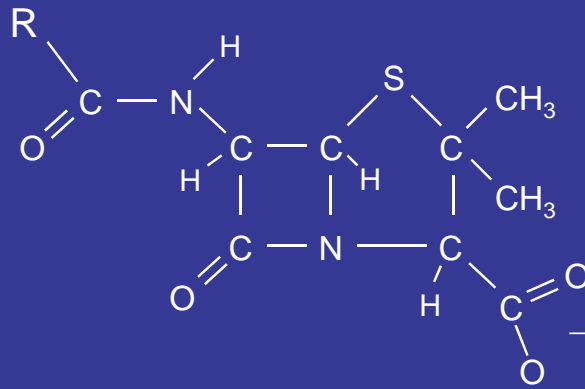
Thiazolidine Ring

Penicillin

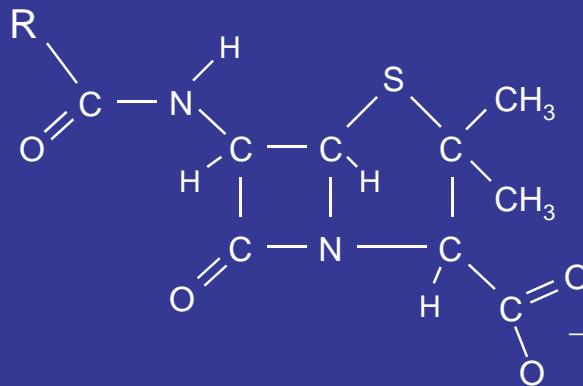


Penicillin G

Penicillin



Penicillin



- Original strain (Fleming) produced penicillin at 1.2 mg/L. Current strains produce penicillin at 50 g/L.
- Inhibitor of bacterial cell wall synthesis
- Inhibits transpeptidase and alanine carboxypeptidase
- Very low mammalian toxicity
- Extremely unstable

Penicillin

Original motivation was just to produce enough penicillin for the war effort. Used bran surface cultures - slow, impractical, with low productivity.

<http://www.youtube.com/watch?v=UJ6KTKVxkcM>

<https://www.youtube.com/watch?v=896YNIWxZI0>

Engineering challenges for submerged cultures:

- 1) Need sterilizable tanks, seals, piping, valves, etc.
- 2) Need high flowrate of sterile, clean air (1.0 vvm max)
- 3) Need large agitators to dissolve oxygen from air
- 4) Need to remove heat from metabolism and agitation
- ~~5) Need recovery operation (i.e., purify 1.2 mg/L penicillin)~~

Beyond the scope of this course

1934 **Gautheret** successfully cultured plant cells.

1940s Streptomycins
Vitamin B12 (still exclusively produced by fermentation)

1950s Cortisone (\$200/g → \$16/g)
Polio and pertussis vaccines

1960s Xanthan gum
Alkaline proteases (detergents)
<http://www.youtube.com/watch?v=x4q1qXX4yhI>
<http://www.youtube.com/watch?v=2xPG1KXfUwU>

1970s Glucose isomerase for production of HFCS
Kohler and **Milstein** develop monoclonal antibodies.

1980s Poly(hydroxybutyrate)

- 1990s Lysine, Threonine, Isoleucine
Antibodies
Lactic Acid (rebirth)
- 2000s 1,2 - Propanediol
Xylitol
Hydroxypropanoic acid (OPX Biotechnologies)
- 2010s 1,4 – Butanediol (Genomatica)
Succinate (Myriant, BioAmber, BASF)