Sequence Coordinates
0- vs 1- base

Bob Milius, PhD
Bioinformatics Research
NMDP®/Be The Match®

Two Things

1. **How do we number the sequence?**
   - start with 0 or 1 ?

2. **What do we include?**
   - Position includes the thing
     - Inclusive
     - Closed
     - [ ]
   - Position excludes the thing
     - Exclusive
     - Open
     - ( )
   - Example: these all mean the same thing
     - 0-base inclusive start, exclusive end
     - 0-base, half open
     - [0,)

Two major systems in use

```
1-base  12345678
        CAGGAGCA
0-base  01234567
```

- **1-base, inclusive start, inclusive end**
  - Describing entire sequence : start = 1, end = 8
    - [1,8]
  - Describing GGAG subsequence: start = 3, end =6
    - [3,6]

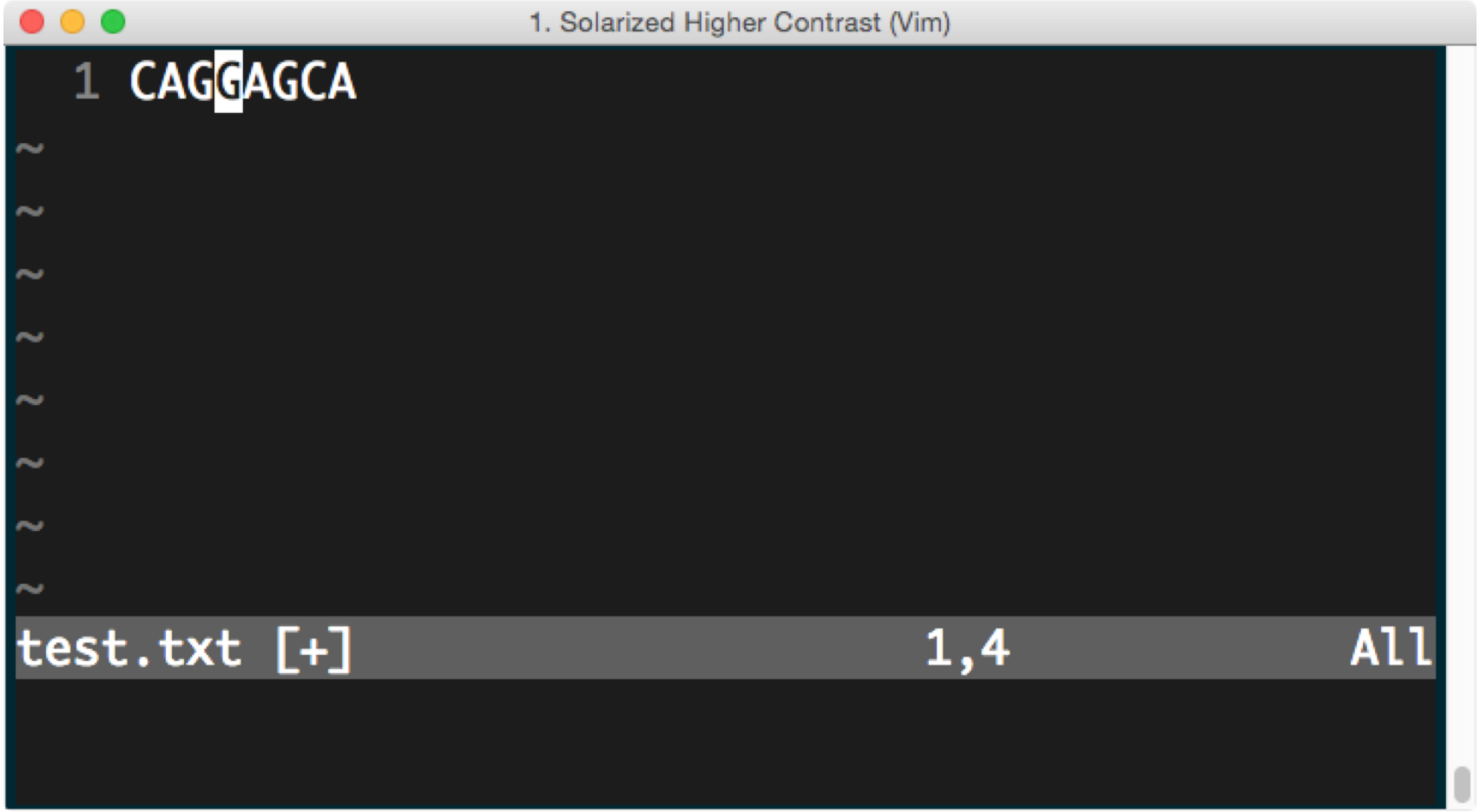
- **0-base, inclusive start, exclusive end**
  - Describing entire sequence: start = 0, end = 8
    - [0,8]
  - Describing GGAG subsequence: start = 2, end = 6
    - [2,6)

Another way to think of it: character vs interval counting

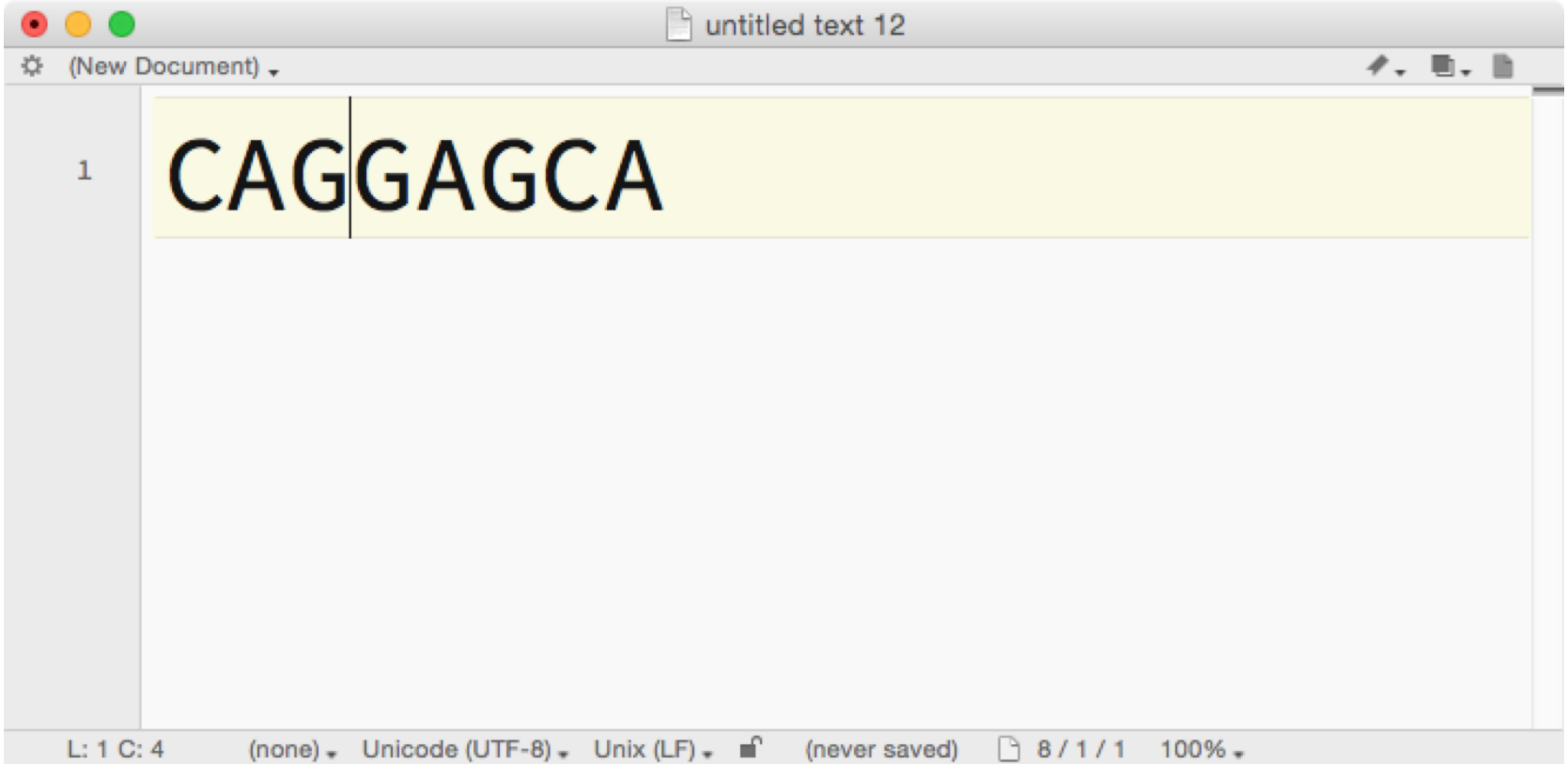
```
character   1 2 3 4 5 6 7 8
            | | | | | | | |
            C A G G A G C A
           | | | | | | | | |
interval   0 1 2 3 4 5 6 7 8
```

- Character = counts each base
- Interval = counts the spaces between each base
  - Also known as interbase counting

Character based



Interval based



1-base, inclusive start, inclusive end

- Easier for humans to understand – it's how we think
- Many systems use this already
  - HGVS
  - VCF
  - ClinVar (uses HGVS)
  - Genbank files
  - UCSC genome browser
  - IPD-IMGT/HLA
- Akin to cursor position in early text editors
- Programming a little tricky
  - need to add or subtract 1 to calculations
  - length = end – start + 1

0-base, inclusive start, exclusive end (interval counting)

- Easier for computers to consume
- Many systems use this already
  (mostly newer and backend systems)
  - Global Alliance for Genomics and Health (GA4GH) API
  - ClinGen Data Model
  - Genbank database & ASN files
  - BED, BAM files
  - UCSC database
  - HML 1.0
- Akin to cursor positioning in modern text editors
- Programming easier
  - length = end – start

What Do Programming Languages Use for Array Indexing?

- 1-based
  - FORTRAN, SASL, MATLAB, Smalltalk
- 0-based
  - C, Perl, Python, Java, Ruby, JavaScript

Easy to convert if all we are talking about is sequences and subsequences

```
character   1 2 3 4 5 6 7 8
            | | | | | | | |
            C A G G A G C A
           | | | | | | | | |
interval   0 1 2 3 4 5 6 7 8
```

Character → Interval = subtract 1 from start

- Character (1-base)
  - Start = 3
  - End = 6
  - [3,6]
- Interval (0-base)
  - Start = 2
  - End = 6
  - [2,6)

But trickier when describing variations

```
character   1 2 3 4 5 6 7 8          1 2 3 4 5 6 7 8 9
            | | | | | | | |          | | | | | | | | |
            C A G G A G C A    →     C A T G G A G C A
           | | | | | | | | |       | | | | | | | | | |
interval   0 1 2 3 4 5 6 7 8         0 1 2 3 4 5 6 7 8 9
```

- How to describe an insertion?
- **Character**: If we say the insertion happen at position 3, we need to know if the insertion is before or after that position
  - If we have a rule that insertions are before a position, then we can put insertions at the beginning of a sequence but not the end.
  - Use substitution: eg. describe a substitution at position 3 from G to TG
  - HGVS and VCF have different rules in describing variants
- **Interval**: insertions are easily described, it happens in the space between the positions

Great discussion describing variants with different coordinate systems

http://datamodel.clinicalgenome.org/development/allele/discussion/coordinate_numbering.html

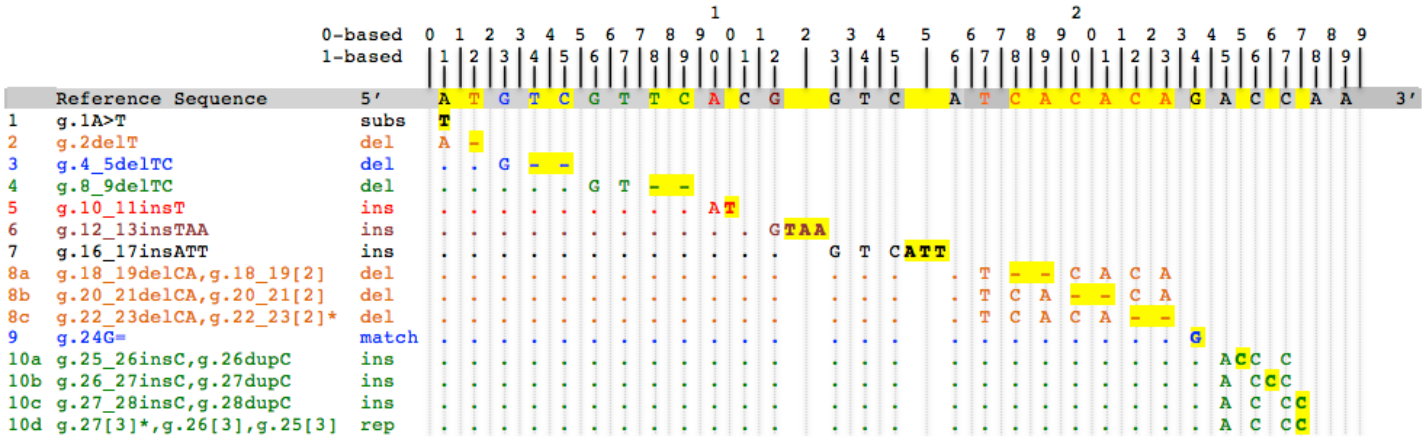
- The Alignment Method
  - Based on the numbering used in VCF
- The Variant Method
  - Based on the numbering used in HGVS expressions

1-base

- The Interval Method
  - Based on numbering intervals as in BED files

0-base

How the different methods describe variation



	HGVS	Alignment Format (1-based)				Variant Format (1-based)				Interval Format (0-based)			
		Start	End	Ref Allele	Alt Allele	Start	End	Ref Allele	Alt Allele	Start	End	Ref Allele	Alt Allele
1	g.1A>T	1	1	A	T	1	1	A	T	0	1	A	T
2	g.2delT	1	2	AT	A	2	2	T	-	1	2	T	-
3	g.4_5delTC	3	5	GTC	G	4	5	TC	-	3	5	TC	-
4	g.8_9delTC	6	9	GTTC	GT	8	9	TC	-	7	9	TC	-
5	g.10_11insT	10	10	A	AT	10	11	-	T	10	10	-	T
6	g.12_13insTAA	12	12	G	GTAA	12	13	-	TAA	12	12	-	TAA
7	g.16_17insATT	13	15	GTC	GTCATT	15	16	-	ATT	15	15	-	ATT
8a	g.18_19delCA,g.18_19[2]	17	19	TCA	T	18	19	CA	-	17	19	CA	-
8b	g.20_21delCA,g.20_21[2]	17	21	TCACA	TCA	20	21	CA	-	19	21	CA	-
8c	g.22_23delCA,g.22_23[2]*	17	23	TCACACA	TCACA	22	23	CA	-	21	23	CA	-
9	g.24G=	24	24	G	G	24	24	G	G	23	24	G	G
10a	g.25_26insC,g.26dupC	25	26	A	AC	25	26	-	C	25	25	-	C
10b	g.26_27insC,g.27dupC	26	27	C	CC	26	27	-	C	26	26	-	C
10c	g.27_28insC,g.28dupC	27	28	C	CC	27	28	-	C	27	27	-	C
10d	g.27[3]*,g.26[3],g.25[3]	27	27	C	CC	27	28	-	C	27	27	-	C

* These are the HGVS recommended representation for the canonically equivalent representations of item 8 and 10, respectively. These representations may appear in practice, but should be canonicalized so that they are seen as the same. HGVS recommends a right-justified representation and VCF recommends a left-justified representation, but neither is guaranteed.

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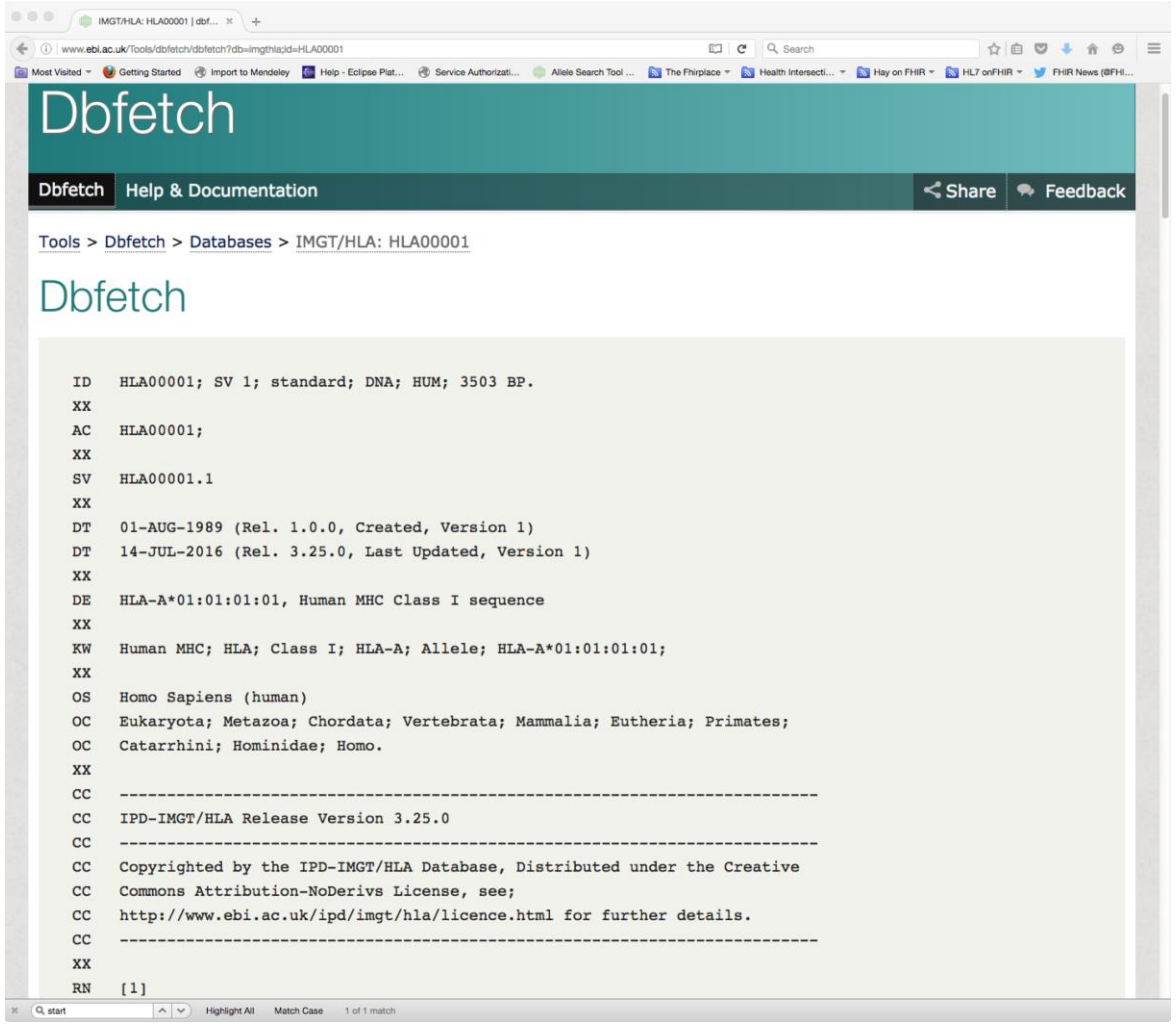
http://datamodel.clinicalgenome.org/development/allele/discussion/coordinate_numbering.html

If you are using IPD-IMGT/HLA as a reference…



http://www.ebi.ac.uk/Tools/dbfetch/dbfetch?db=imgthla;id=HLA00001

If you are using IPD-IMGT/HLA as a reference…

```
FT                   /cell_line="PP"
FT   CDS             join(301..373,504..773,1015..1290,1870..2145,2248..2364,
FT                   2807..2839,2982..3029,3199..3203)
FT                   /codon_start=1
FT                   /gene="HLA-A"
FT                   /allele="HLA-A*01:01:01:01"
FT                   /product="MHC Class I HLA-A*01:01:01:01 sequence"
FT                   /translation="MAVMAPRTLLLLLSGALALTQTWAGSHSMRYFFTSVSRPGRGEPR
FT                   FIAVGYVDDTQFVRFDSDAASQKMEPRAPWIEQEGPEYWDQETRNMKAHSQTDRANLGT
FT                   LRGYYNQSEDGSHTIQIMYGCDVGPDGRFLRGYRQDAYDGKDYIALNEDLRSWTAADMA
FT                   AQITKRKWEAVHAAEQRRVYLEGRCVDGLRRYLENGKETLQRTDPPKTHMTHHPISDHE
FT                   ATLRCWALGFYPAEITLTWQRDGEDQTQDTELVETRPAGDGTFQKWAAVVVPSGEEQRY
FT                   TCHVQHEGLPKPLTLRWELSSQPTIPIVGIIAGLVLLGAVITGAVVAAVMWRRKSSDRK
FT                   GGSYTQAASSDSAQGSDVSLTACKV"
FT   UTR             1..300
FT   exon            301..373
FT                   /number="1"
FT   intron          374..503
FT                   /number="1"
FT   exon            504..773
FT                   /number="2"
FT   intron          774..1014
FT                   /number="2"
FT   exon            1015..1290
FT                   /number="3"
FT   intron          1291..1869
FT                   /number="3"
FT   exon            1870..2145
FT                   /number="4"
FT   intron          2146..2247
FT                   /number="4"
FT   exon            2248..2364
FT                   /number="5"
FT   intron          2365..2806
FT                   /number="5"
FT   exon            2807..2839
FT                   /number="6"
FT   intron          2840..2981
```

http://www.ebi.ac.uk/Tools/dbfetch/dbfetch?db=imgthla;id=HLA00001

From IPD-IMGT/HLA to 0-base

```
FT   UTR       1..300
FT   exon      301..373
FT             /number="1”
FT   intron    374..503
FT             /number="1”
FT   exon      504..773
FT             /number="2”
FT   intron    774..1014
FT             /number="2”
FT   exon      1015..1290
FT             /number="3”
FT   intron    1291..1869
FT             /number="3”
FT   exon      1870..2145
FT             /number="4”
FT   intron    2146..2247
FT             /number="4”
FT   exon      2248..2364
FT             /number="5”
FT   intron    2365..2806
FT             /number="5”
FT   exon      2807..2839
FT             /number="6”
FT   intron    2840..2981
FT             /number="6”
FT   exon      2982..3029
FT             /number="7”
FT   intron    3030..3198
FT             /number="7”
FT   exon      3199..3203
FT             /number="8”
FT   UTR       3204..3503
```

```
FT   UTR       0..300
FT   exon      300..373
FT             /number="1”
FT   intron    373..503
FT             /number="1”
FT   exon      503..773
FT             /number="2”
FT   intron    773..1014
FT             /number="2”
FT   exon      1014..1290
FT             /number="3”
FT   intron    1290..1869
FT             /number="3”
FT   exon      1869..2145
FT             /number="4”
FT   intron    2145..2247
FT             /number="4”
FT   exon      2247..2364
FT             /number="5”
FT   intron    2364..2806
FT             /number="5”
FT   exon      2806..2839
FT             /number="6”
FT   intron    2840..2981
FT             /number="6”
FT   exon      2981..3029
FT             /number="7”
FT   intron    3029..3198
FT             /number="7”
FT   exon      3198..3203
FT             /number="8”
FT   UTR       3203..3503
```

From IPD-IMGT/HLA to 0-base

```
FT   UTR       1..300
FT   exon      301..373
FT             /number="1”
FT   intron    374..503
FT             /number="1”
FT   exon      504..773
FT             /number="2”
FT   intron    774..1014
FT             /number="2”
FT   exon      1015..1290
FT             /number="3”
FT   intron    1291..1869
FT             /number="3”
FT   exon      1870..2145
FT             /number="4”
FT   intron    2146..2247
FT             /number="4”
FT   exon      2248..2364
FT             /number="5”
FT   intron    2365..2806
FT             /number="5”
FT   exon      2807..2839
FT             /number="6”
FT   intron    2840..2981
FT             /number="6”
FT   exon      2982..3029
FT             /number="7”
FT   intron    3030..3198
FT             /number="7”
FT   exon      3199..3203
FT             /number="8”
FT   UTR       3204..3503
```

```
FT   UTR       0..300
FT   exon      300..373
FT             /number="1”
FT   intron    373..503
FT             /number="1”
FT   exon      503..773
FT             /number="2”
FT   intron    773..1014
FT             /number="2”
FT   exon      1014..1290
FT             /number="3”
FT   intron    1290..1869
FT             /number="3”
FT   exon      1869..2145
FT             /number="4”
FT   intron    2145..2247
FT             /number="4”
FT   exon      2247..2364
FT             /number="5”
FT   intron    2364..2806
FT             /number="5”
FT   exon      2806..2839
FT             /number="6”
FT   intron    2840..2981
FT             /number="6”
FT   exon      2981..3029
FT             /number="7”
FT   intron    3029..3198
FT             /number="7”
FT   exon      3198..3203
FT             /number="8”
FT   UTR       3203..3503
```

Exon 2 of HLA-A*01:01:01:01 (HLA00001.1)

CACATCCGTGTCCCGGCCCGGCCGCGGGGAGCCCCGCTTCATCG
CCGTGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGC
GACGCCGCGAGCCAGAAGATGGAGCCGCGGGCGCCGTGGATAGA
GCAGGAGGGGCCGGAGTATTGGGACCAGGAGACACGGAATATGA
AGGCCCACTCACAGACTGACCGAGCGAACCTGGGGACCCTGCGC
GGCTACTACAACCAGAGCGAGGACG

- IPD-IMGT/HLA (uses 1-base)
  - start =504, end=773
  - [504,773]
- In HML (uses 0-base, interval)
  - start= 503, end= 773
  - [503,773)

Describing a reference from IPD-IMGT/HLA in HML 1–base to 0-base conversion

```
<consensus-sequence date="2016-09-01">
    <reference-database
        name="IPD-IMGT/HLA”
        description="IPD-IMGT/HLA Database”
        version="3.25”
        availability="public”
        curated="true”
        uri="http://www.ebi.ac.uk/ipd/imgt/hla/" >
        <reference-sequence
            id="ref1”
            name="HLA-A*01:01:01:01”
            start="0" end="3503”
            accession="HLA00001.1”
            uri="http://www.ebi.ac.uk/Tools/dbfetch/dbfetch?db=imgthla;id=HLA00001.1"/>
    </reference-database>
    <consensus-sequence-block
        reference-sequence-id="ref1”
        start="503" end="773”
        description=”Exon 2 of HLA-A*01:01:01:01”
        phase-set="1">
        <sequence>
CACATCCGTGTCCCGGCCCGGCCGCGGGGAGCCCCGCTTCATCGCCGTGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGCGACGCCGCGAGCCAGAAGATGGAGCCGCG
GGCGCCGTGGATAGAGCAGGAGGGGCCGGAGTATTGGGACCAGGAGACACGGAATATGAAGGCCCACTCACAGACTGACCGAGCGAACCTGGGGACCCTGCGCGGCTACTACAACCA
GAGCGAGGACG
        </sequence>
    </consensus-sequence-block>
</consensus-sequence>
```

Describing a reference from IPD-IMGT/HLA in HML 1–base to 0-base conversion

```
<reference-sequence
    id="ref1”
    name=" HLA-A*01:01:01:01”
    start="0" end="3503”
    accession="HLA00001.1”
    uri="http://www.ebi.ac.uk/Tools/dbfetch/dbfetch?db=imgthla;id=HLA00001.1"/>
</reference-database>
<consensus-sequence-block
    reference-sequence-id="ref1”
    start="503" end="773”
    description=”Exon 2 of HLA-A*01:01:01:01”
    phase-set="1">
    <sequence>CACATCCGTG…GGACG</sequence>
</consensus-sequence-block>
```

Exon 2 of HLA-A*01:01:01:01 (HLA00001.1) with C➔T substitution

CA**T**ATCCGTGTCCCGGCCCGGCCGCGGGGAGCCCCGCTTCATCG
CCGTGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGC
GACGCCGCGAGCCAGAAGATGGAGCCGCGGGCGCCGTGGATAGA
GCAGGAGGGGCCGGAGTATTGGGACCAGGAGACACGGAATATGA
AGGCCCACTCACAGACTGACCGAGCGAACCTGGGGACCCTGCGC
GGCTACTACAACCAGAGCGAGGACG

- **SequenceBlock is always relative to the reference**
- In HML (uses 0-base, interval)
  - start= **503**, end= **773**

Exon 2 of HLA-A*01:01:01:01 (HLA00001.1) with C➔T substitution

```
CATATCCGTGTCCCGGCCCGGCCGCGGGGAGCCCCGCTTCATCG
CCGTGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGC
GACGCCGCGAGCCAGAAGATGGAGCCGCGGGCGCCGTGGATAGA
GCAGGAGGGGCCGGAGTATTGGGACCAGGAGACACGGAATATGA
AGGCCCACTCACAGACTGACCGAGCGAACCTGGGGACCCTGCGC
GGCTACTACAACCAGAGCGAGGACG
```

- **SequenceBlock is always relative to the reference**
- In HML (uses 0-base, interval)
  - start= **503**, end= **773**

```
<variant
  reference-bases="C"
  alternate-bases="T"
  start="505" end="506"/>
```

Describing a reference from IPD-IMGT/HLA in HML 1–base to 0-base conversion

```
<reference-sequence
    id="ref1”
    name=" HLA-A*01:01:01:01”
    start="0" end="3503”
    accession="HLA00001.1”
    uri="http://www.ebi.ac.uk/Tools/dbfetch/dbfetch?db=imgthla;id=HLA00001.1"/>
</reference-database>
<consensus-sequence-block
    reference-sequence-id="ref1”
    start="503" end="773”
    description=”Exon 2 of HLA-A*01:01:01:01”
    phase-set="1">
    <sequence>CACATCCGTG…GGACG</sequence>
    <variant reference-bases=”C" alternate-bases=”T" start=”505" end=”506">
</consensus-sequence-block>
```

Exon 2 of HLA-A*01:01:01:01 (HLA00001.1) with C deletion

CA**CA**TCCGTGTCCCGGCCCGGCCGCGGGGAGCCCCGCTTCATCG

CCGTGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGC

GACGCCGCGAGCCAGAAGATGGAGCCGCGGGCGCCGTGGATAGA

GCAGGAGGGGCCGGAGTATTGGGACCAGGAGACACGGAATATGA

AGGCCCACTCACAGACTGACCGAGCGAACCTGGGGACCCTGCGC

GGCTACTACAACCAGAGCGAGGACG

- **consensus-sequence-block coordinate is always relative to the reference**
- In HML (uses 0-base, interval)
  - start= **503**, end= **773**

Exon 2 of HLA-A*01:01:01:01 (HLA00001.1) with C deletion

CA**A**TCCGTGTCCCGGCCCGGCCGCGGGGAGCCCCGCTTCATCG

CCGTGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGC

GACGCCGCGAGCCAGAAGATGGAGCCGCGGGCGCCGTGGATAGA

GCAGGAGGGGCCGGAGTATTGGGACCAGGAGACACGGAATATGA

AGGCCCACTCACAGACTGACCGAGCGAACCTGGGGACCCTGCGC

GGCTACTACAACCAGAGCGAGGACG

- **consensus-sequence-block coordinate is always <u>relative to the reference</u>**
- In HML (uses 0-base, interval)
  - start= **503**, end= **773**

```
<variant
  reference-bases="CA"
  alternate-bases="A"
  start="505" end="507"/>
```

We treat this deletion as a substitution

Describing a reference from IPD-IMGT/HLA in HML 1–base to 0-base conversion

```
<reference-sequence
    id="ref1”
    name=" HLA-A*01:01:01:01”
    start="0" end="3503”
    accession="HLA00001.1”
    uri="http://www.ebi.ac.uk/Tools/dbfetch/dbfetch?db=imgthla;id=HLA00001.1"/>
</reference-database>
<consensus-sequence-block
    reference-sequence-id="ref1”
    start="503" end="773”
    description=”Exon 2 of HLA-A*01:01:01:01”
    phase-set="1">
    <sequence>CACATCCGTG…GGACG</sequence>
    <variant reference-bases=”CA" alternate-bases=”A" start=”505" end=”507">
</consensus-sequence-block>
```

A word about what's allowed in <sequence> in HML

```
<xs:simpleType name="iupac-bases">
   <xs:annotation>
     <xs:documentation>
        Nucleotide bases representing sequence ambiguity. Primary nucleotides: A, C, G,
        T  (DNA). "Wildcard" nucleotides: M, R, W, S, Y, K, V, H, D, B, X, N. Wildcard
        nucleotides may be used if they are acceptable in the context in which they
        appear. The default is to use all upper case letters. The full specification of
        the IUPAC codes may be found here:
        (http://nar.oxfordjournals.org/content/13/9/3021.short) Cornish-Bowden A.
        Nomenclature for incompletely specified bases in nucleic acid sequences:
        recommendations 1984. Nucleic Acids Res. 1985; 13:3021-3030. The bases of the
        sequence string are restricted to the upper and lower case versions of the
        nucleotides specified above. Data: ---- - Nucleotide sequence in DNA alphabet
        (string, required)
      </xs:documentation>
   </xs:annotation>
   <xs:restriction base="xs:string">
      <xs:pattern value="([\sACGTUMRWSYKVHDBXNacgtumrwsykvhdbxn])+"/>
      <xs:minLength value="1"/>
   </xs:restriction>
</xs:simpleType>
```

No gaps!!

Things to remember

- HML 1.0 uses the 0-base, interval counting system
- To convert a 1-base, closed system to 0-based interval, just subtract 1 from the start
- Reference sequence must be gapless, unambiguous, and can be easily dereferenced
- Consensus-sequence-block coordinates are relative to the reference coordinates
- Variant coordinates are relative to the reference coordinates
- Variations are treated as substitutions
- Given a reference sequence, and a window into that reference, and a variant description in that window, we can easily reconstruct the actual sequence being reported

More reading…

- ClinGen discussion on coordinate numbering
  - http://datamodel.clinicalgenome.org/development/allele/discussion/coordinate_numbering.html
- Question: What Are The Advantages/Disadvantages Of One-Based Vs. Zero-Based Genome Coordinate Systems
  - https://www.biostars.org/p/6373/
- Tutorial: Cheat Sheet For One-Based Vs Zero-Based Coordinate Systems
  - https://www.biostars.org/p/84686/
- Coordinate Transforms
  - http://genomewiki.ucsc.edu/index.php/Coordinate_Transforms
- Genome Coordinate Conventions
  - http://alternateallele.blogspot.com/2012/03/genome-coordinate-conventions.html
- Genome Coordinate Cheat Sheet
  - http://alternateallele.blogspot.com/2012/03/genome-coordinate-cheat-sheet.html

And more…

- Global Alliance for Genomics and Health (GA4GH)
  - Discussion
    - https://github.com/ga4gh/schemas/issues/121
  - API
    - https://ga4gh-schemas.readthedocs.io/en/latest/schemas/common.proto.html
  -

- Ensembl is using the GA4GH API as part of it RESTful services
  - https://rest.ensembl.org/documentation/info/gavariants

Thank you!

Questions?